# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208379Orig1s000

# NON-CLINICAL REVIEW(S)

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

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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|---|---|
| **NDA NUMBER**: | 208379 |
| **REVIEW NUMBER:** | 2 |
| **SUPPORTING DOCUMENTS:** | SN0013 (SD 14) and 0016 (SD 17) |
| **APPLICANT'S LETTER DATE:** | 1/17/2017 and 3/6/2017, respectively |
| **CDER STAMP DATE:** | 1/17/2017 and 3/6/2017, respectively |
| **PRODUCT**: | Pitavastatin Magnesium |
| **INDICATION**: | Indicated for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia |
| **APPLICANT**: | Zydus Pharmaceuticals, Inc, Pennington, NJ, a wholly owned subsidiary of the parent company, Cadila Healthcare Limited, India |
| **REVIEW DIVISION**: | Division of Metabolism and Endocrinology Products |
| **REVIEWER**: | Indra Antonipillai, PhD |
| **SUPERVISOR**: | C. Lee Elmore, PhD |
| **DIVISION DIRECTOR**: | Jean-Marc Guettier, MDCM |
| **PROJECT MANAGER**: | Richard Whitehead |

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# 1 Executive Summary

## 1.1 Introduction

Pitavastatin is a cholesterol lowering statin drug, belonging to the 'HMG-CoA reductase inhibitor' established pharmacologic class. Zydus Pharmaceuticals (the Applicant) has resubmitted a 505(b)(2) NDA application intending to market Pitavastatin Magnesium at the same dosage strengths (i.e., 1 mg, 2 mg, and 4 mg) as the Orange book listed drug Livalo (pitavastatin calcium, marketed under NDA 022363). Pitavastatin Magnesium is intended for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia.

## 1.2 Brief Discussion of Nonclinical Findings

In the original NDA submission, the Applicant provided a 4-week bridging study in rats comparing the toxicity of Pitavastatin Magnesium with that demonstrated by the listed drug Livalo. The submitted study was adequate for the proposed use of Pitavastatin Magnesium; the original application was recommended for approval, from the Pharmacology/Toxicology point of view. Refer to the original Pharmacology/Toxicology NDA review, signed in DARRTS on 11/24/2015.

For this class-2 NDA resubmission, no new nonclinical data were submitted, although this resubmission did trigger a requirement for updated product labeling as specified by the Pregnancy and Lactation Labeling Rule (PLLR). The Applicant's proposed labeling, as submitted, is compliant with PLLR and, with the exception of the different trade name, is identical to PLLR-compliant labeling for the listed drug.

## 1.3 Recommendations

### 1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this application for proposed indication.

### 1.3.3 Labeling

The proposed Pitavastatin Magnesium labeling relevant to PLLR is identical to that of the listed drug Livalo, except that the word Livalo has been replaced with "ZYPITAMAG". No labeling changes are recommended. See the draft label provided by the Applicant (copied below from submission serial number 0016 (SD 17, dated 3/6/17).

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

*Risk Summary*

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

pitavastatin during organogenesis at exposures which were 22 times and 4 times, respectively, the maximum recommended human dose (MRHD) [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

Animal Data

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤ 36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation.

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3 mg/kg/day, 10 mg/kg/day, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.
Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1 mg/kg/day, 0.3 mg/kg/day, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

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

**8.2 Lactation**

Risk Summary
ZYPITAMAG is contraindicated during breastfeeding [see Contraindications (4.4)]. There is no available (b) (4) the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in this class passes into human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ZYPITAMAG.

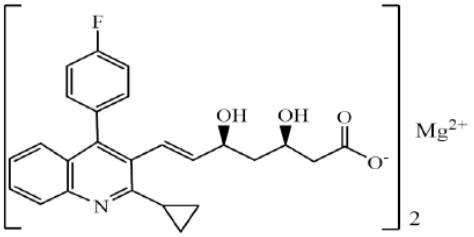
## 2 Drug Information

### 2.1 Drug

**CAS registry number**: 956116-90-8
**Generic name**: ZYPITAMAG (Pitavastatin magnesium)
**Code Name**: NA
**Chemical Name**: (3R,5S)-7-[2-Cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl]3,5-dihydroxy-6(E)-heptanoic acid hemi magnesium

**Molecular formula/molecular weight**: $C_{50}H_{46}MgF_2N_2O_8$ / 865.21.

**Structure or Biochemical Description**:




Pitavastatin Magnesium

**Pharmacologic Class**: HMG-CoA reductase inhibitor

### 2.2 Relevant INDs, NDAs, and DMFs

Pitavastatin magnesium (IND 117,674 / DMF (b) (4) Pitavastatin calcium (marketed by Kowa under NDA 022363 as Livalo).

### 2.3 Drug Formulation:

Pitavastatin Magnesium is formulated as oral tablets. For details, see the original NDA review in DARRTS.

### 2.4 Comments on Novel Excipients

See the original NDA review in DARRTS.

### 2.5 Comments on Impurities/Degradants of Concern

See the original NDA review in DARRTS.

### 2.6 Proposed Clinical Population and Dosing Regimen

The drug is indicated for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), LDL-C, Apo B and triglycerides (TG), over the dose range of 1 to 4 mg daily. The maximum daily dose is 4 mg.

**2.7 Regulatory Background**:

The original application was submitted on 3/31/2015, Pharmacology /Toxicology recommended approval of the application. However, on 1/26/16 the Applicant received a Complete Response Letter from the Agency for facility inspection issues, which stated in part:

*"We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues*

On 1/17/17, Zydus Pharmaceuticals (USA) Inc. provided a class 2 re-submission with, considered a Complete Response to address the comments listed in the Agency's complete Response letter, sent to them on 1/26/2016.

On 2/13/17 an e-mail was sent to the sponsor, requesting a formal review and summary of the available clinical and nonclinical information to support the changes in the 'Pregnancy, Lactation, and Females and Males of Reproductive Potential' sections of label, which was absent from the application resubmission.

On 3/6/17, the Applicant provided the aforementioned information (supporting document # 17).

**3 Studies Submitted**

**3.1 Studies Reviewed**

In the current resubmission, the sections of the label relevant to PLLR labeling are reviewed. In the submission dated 3/6/17, the Applicant states that "*they have not conducted any additional clinical and nonclinical study to demonstrate the effect of pitavastatin in Pregnancy, Lactation, and in Females and Males of Reproductive Potential. The information provided in the package insert submitted on January 17, 2017 is in line with the latest approved labeling, i.e., LIVALO® (pitavastatin)."*

However, the Applicant has provided some published non-clinical information on male and female fertility, developmental and reproductive toxicity, and lactation studies (submission date 3/6/2017), but none of that information is new and therefore those studies are not reviewed here.

Note that a Pharmacology/Toxicology review was already signed in DARRTS when this resubmission was submitted; therefore only the sections of the labeling, relevant to PLLR are reviewed here.

**4. Pharmacology / General Toxicology**

Please refer to the review signed in DARRTS on 11/24/2015.

**11. Integrated Summary and Safety Evaluation**

When the original application was submitted, Zydus Pharmaceuticals had performed a 28-day bridging toxicity study in rats, comparing its Pitavastatin product to the reference drug Livalo. This 28-day toxicity study demonstrated that the two products are sufficiently comparable. No new concerning toxicities were identified in the Pitavastatin Magnesium-treated groups. From the Pharmacology/Toxicology standpoint, approval of this application is recommended.

**Labeling Review**: The label has been submitted according to PLLR requirements. The sections of the label for Pitavastatin Magnesium relevant to PLLR are identical to the comparable sections in the approved drug product labeling for NDA 022363, Livalo (pitavastatin calcium). In the current application, the submitted label was reviewed; the applicant has replaced the word "Livalo" with their own proprietary name "ZYPITAMAG". The rest of the labeling text is identical to the innovator's label.

**Recommendation:** From the Pharmacology/Toxicology point of view, this application is recommended for approval. The label is acceptable. For additional information, refer to the full review signed in DARRTS on 11/23/2015.

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

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/s/

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INDRA ANTONIPILLAI
04/24/2017
Pharmacology/Toxicology recommends approval of this application for proposed indication.

CALVIN L ELMORE
04/24/2017
I concur.

**Signed off in DARRTS on 11/24/2015**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
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# PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

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|---|---|
| NDA NUMBER: | 208379 |
| SERIAL NUMBER: | 000 |
| DATE RECEIVED BY CENTER: | 3/31/2015 |
| PRODUCT: | Pitavastatin Magnesium |
| INTENDED CLINICAL POPULATION: | Indicated for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia. |
| SPONSOR: | Zydus Pharmaceuticals Inc, Pennington, NJ is a wholly owned subsidiary of the parent company, Cadila Healthcare Limited, India. |
| DOCUMENTS REVIEWED: | e-CTD submission**.** |
| REVIEW DIVISION: | Division of Metabolism and Endocrinology Products |
| PHARM/TOX REVIEWER: | Indra Antonipillai |
| PHARM/TOX SUPERVISOR: | Calvin Elmore |
| DIVISION DIRECTOR: | Jean Marc Guettier |
| PROJECT MANAGER: | Martin White |
| Date of review submission to DARRTS: | 11/23/2015 |

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## *EXECUTIVE SUMMARY*

### I. Recommendations

A. **Recommendation on approvability**: Pharmacology/Toxicology recommends approval of this application.

B. **Recommendation for Nonclinical Studies**: No additional preclinical studies are required for this drug product. In the current application, sponsor has provided a 4-week bridging toxicity study in rats with their proposed drug product and a reference listed drug Livalo. The submitted studies are adequate for proposed use of Pitavastatin magnesium and provide a bridge to the Agency's prior approval decision of reference drug product Livalo.

C. **Recommendations on labeling**: No pharmacology /toxicology labeling changes are recommended. The label should be identical to the Livalo label, except that the word Livalo should be replaced with "ZYPITAMAG". See the draft label on pages 58-61.

### II. Summary of non-clinical findings

A. **Brief overview of nonclinical findings**: Pitavastatin calcium is currently marketed by Kowa Co., LTD, under NDA 022363 (referred to this application as Livalo). The current Pitavastatin magnesium is being developed by Zydus Pharmaceuticals for the same indication at the same dosage strengths as the marketed product Livalo (maximum dose of 4 mg), for a 505(b)(2) application. In a 28-day oral gavage toxicity study in rats, doses of 0 (vehicle), 0 (crushed placebo tablet), 2, 5, 10 mg/kg/day of the Pitavastatin magnesium as crushed tabletswere administered to rats. An additional 3 groups of rats were similarly administered the reference drug Livalo (2, 5, 10 mg/kg/day) for comparison. The plasma exposures (AUC) of Pitavastatin magnesium in general were similar to that of Livalo (with the exception of the HD of Livalo in females). On Day-28 the AUC exposures with pitavastatin magnesium in males/ females were 859/630, 3522/2956, 7521/6893 ng.h/ml at 1, 5, and 10 mg/kg/day respectively (vs with Livalo, which were 647/837, 3823/3389, 6172/10849 ng.h/ml respectively). In males at the HD of Zydus's Pitavastatin magnesium, body weight gains were lower in recovery group vs the controls (13.7* vs 16.6 g with controls, *p<0.05) but not with the listed drug (Livalo). In extensive neuro-behavioral functional observations in males, decreased hind-limb foot splay was noted at a HD of Zydus Pitavastatin magnesium and at MD of Livalo vs controls (71.7*, 64.4* vs 89.3 mm, *p<0.05). At the end of the drug free recovery period, the hind-limb foot splay was still decreased at a HD of Zydus Pitavastatin, but not with Livalo (62.8* vs 76.5 mm, *p<0.01). Histopathology findings at a HD of 10 mg/kg/day with the pitavastatin magnesium and Livalo were in general similar, i.e. both products produced lesions in the non-glandular stomach (for combined males+females, the incidences were 0/40 0/20, 11/20, 19/20 vs 0/40, 2/20, 17/20, 19/20 with Livalo at 0, 2, 5, 10 mg/kg/day respectively). Subtle findings were noted in male rats administered Pitavastatin magnesium, which were not seen with Livalo. These included histopathology findings in the adrenals (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex in 1/10 vs 0/10 with Livalo). In females, no significant toxicity was noted in the other organs. Note that minimal findings noted above at a high dose (of 10 mg/kg/day) do not represent toxicological meaningful differences between Pitavastatin magnesium and the listed drug Livalo, and there is a substantial safety margin, as these occurred at 24-fold the human therapeutic dose of 4 mg/day. The total impurities present in the drug product are qualified, as the levels tested in the 28-day toxicity study with Pitavastatin magnesium were up to (b) (4) and proposed specification are for

up to [redacted] (b) (4) assuming 60 kg average weight of an adult). The NOAEL dose for the Pitavastatin mgnesium in this 28-day oral toxicity study in rats is 2 mg/kg/day, as histopathology findings in the stomach were noted at 5 and 10 mg/kg/day. This NOAEL of 2 mg/kg/day (or 12 mg/m$^2$/day) provides a safety margin of 5 X in human subjects (at the maximal recommended human dose of 4 mg/day or 2.5 mg/m$^2$/day), based on body surface area. From the pharmacology/ toxicology point of view, this application is recommended for approval.

B. **Pharmacologic activity**: Pitavastatin is an HMG-CoA reductase inhibitor (statin). The drug is indicated for treatment of patients with primary hyperlipidemia or mixed dyslipidemia.

C. Nonclinical safety issues relevant to clinical use: None

## *2.6 PHARMACOLOGY/TOXICOLOGY REVIEW*

### 2.6.1 INTRODUCTION AND DRUG HISTORY

**NDA number**: 208-379
**Review number**: 1

**Sequence number/date/type of submission**: 3/31/2015, (#000, original application), 7/6/2015 (#0002, sponsor's response to our pharmacology/toxicology filing communication). This is an eCTD submission. It is a 505(b)(2) application. Sponsor refers to the previous NDA of Pitavastatin calcium or Livalo, approved on 8/3/2009 (by Kowa Company Ltd. USA, NDA 022-363).

**Information to sponsor**: Yes ( ) No (X)
**Sponsor and/or agent**: Zydus Pharmaceuticals Inc, Pennington, NJ. It is a wholly owned subsidiary of the parent company, Cadila Healthcare Limited, India.

**Manufacturer for drug substance**: The drug substance, Pitavastatin Magnesium is manufactured by Cadila Healthcare Limited, Dabhasa, Gujarat, India. It is manufactured according to DMF# (b) (4) (which has been submitted to FDA). A copy of the letter authorizing Zydus Pharmaceuticals to reference to DMF # (b) (4) has been provided.

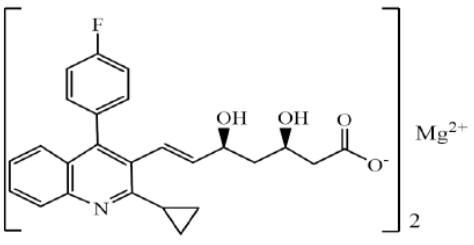
**Reviewer name**: Indra Antonipillai
**Division name**: Division of Metabolism and Endocrinology Products (DMEP).
**Review completion date**: 10/27/2015

**Drug**:

Trade name: Pitavastatin Magnesium (strengths 1, 2, 4 mg tablets)

Generic name: Pitavastatin
Code name: N/A
Chemical name:
(3R,5S)-7-[2-Cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl]3,5-dihydroxy-6(E)-heptanoic acid hemi magnesium

CAS registry number: 956116-90-8
Molecular formula/molecular weight: $C_{50}H_{46}MgF_2N_2O_8$ / 865.21.
Structure:




Pitavastatin Magnesium

**Relevant INDs/NDAs/DMFs**: Pitavastatin magnesium (IND 117,674 / DMF # (b) (4)). Pitavastatin calcium (an approved drug product NDA 022-363/Livalo).

**Drug class**: Statins. Lipid lowering drug product.

**Intended clinical population**: The drug is indicated for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), Apo B and triglycerides (TG), over the dose range of 1 to 4 mg daily. Maximum daily dose is 4 mg.

**Clinical formulation**: The drug substance is manufactured in India, as stated below:

> The drug substance, Pitavastatin Magnesium is manufactured by Cadila Healthcare Limited, Dabhasa, Gujarat, India. Pitavastatin Magnesium has been manufactured according to their Type II DMF (DMF# (b) (4)) currently on file with the FDA. A copy of the DMF letter of authorization permitting Zydus Pharmaceuticals (USA) Inc. to reference DMF # (b) (4) is provided in **Module 1.4.2**. Drug substance manufacturer's cGMP statement is included in this module.

Composition of Pitavastatin magnesium and the reference drug (Livalo) are provided below:

Sponsor states that in the proposed product Pitavastatin magnesium, dis-integrant and alkalizing agents used are different then in the reference drug Livalo, see below:

Qualitative composition of Proposed Product [Pitavastatin Tablets, 1 mg, 2 mg and 4 mg (Magnesium Salt)] and Reference Drug Product [Livalo® (Pitavastatin) Tablets, 1 mg, 2 mg and 4 mg (Calcium Salt)] are provided below;

| Sr. No. | Proposed Product [Pitavastatin Tablets, 1 mg, 2 mg and 4 mg (Magnesium Salt)] | Reference Drug Product [Livalo® (Pitavastatin) Tablets, 1 mg, 2 mg and 4 mg (Calcium Salt)] | Function |
|---|---|---|---|
| 1 | Lactose Monohydrate, NF | Lactose Monohydrate | (b) (4) |
| 2 | Crospovidone, NF (b) (4) | Low substituted hydroxypropyl cellulose | |
| 3 | Hypromellose, USP (b) (4) | Hypromellose | |
| 4 | Sodium Carbonate, NF (Anhydrous Powder) | Magnesium aluminometasilicate | |
| 5 | Calcium Carbonate, NF (b) (4) | - | |
| 6 | Magnesium Stearate, NF | Magnesium stearate | |
| 7 | Coating contains:<br>Hypromellose, USP (b) (4) (b) (4)<br>Titanium Dioxide, USP<br>PEG, (b) (4)<br>Talc, USP (b) (4) | Coating contains:<br>Hypromellose<br>Titanium Dioxide<br>Triethyl citrate<br>Colloidal anhydrous silica | |

*Does not remain in final product, except in traces

(b) (4) (i.e. Crospovidone) and (b) (4) (Sodium Carbonate and Calcium Carbonate) used in proposed product, are different from reference drug product. The proposed formulation contains standard excipients consistent with the design of solid oral dosage form. The amount of an inactive ingredient is well within the level of inactive ingredient database. Further, drug excipient compatibility studies suggested that there was no unusual outcome to finished product; hence employed change(s) doesn't affect the safety or efficacy of the drug product.

**Route of administration**: Oral

**Disclaimer**: The tabular and graphical information is from sponsor's submission unless stated otherwise.

**Studies reviewed within this submission:** In the current submission a 28-day bridging toxicity study in rats with their product and reference drug Livalo, followed by a 14-day drug free recovery period is provided. No gene-toxicity studies have been conducted to qualify the impurities/ excipients/degradants in their drug product. However, in the CMC section, the impurities have been analyzed using QSAR method using ToxTree method. The submitted toxicity study is reviewed here.

### 2.6.1. INTRODUCTION

Pitavastatin belongs to the statin class of drugs for cholesterol lowering therapy. Like other statins, pitavastatin is a selective HMG-CoA reductase inhibitor. Pitavastatin is the *3R,* SS (+)-enantiomer and has two chiral carbon atoms (positions 3 and 5 in the 3,5-dihydroxy-6-heptenoic acid side chain).

Pitavastatin calcium is currently marketed by Kowa Co., LTD. (under NDA 022363/Livalo). Zydus Pharmaceuticals has developed Pitavastatin Magnesium at the same dosage strengths as the currently marketed Livalo (1 mg, 2 mg, and 4 mg), for a proposed 505(b)(2) marketing application.

Here is a brief history on Pitavastatin magnesium drug product

The initial Pre-IND 11767 was submitted to DMEP by the current sponsor on 11/23/2012. Initially the sponsor had proposed to conduct a bridging toxicology study with their product, and with their own formulation of pitavastatin calcium (instead of Livalo). We recommended that the sponsor provide a bridging toxicology study with their pitavastatin magnesium drug substance and compare it directly to Livalo, the listed drug.

On 7/29/2013, following was communicated to the sponsor:

PHARMACOLOGY/TOXICOLOGY
We recommend the use of Livalo as the comparator in your bridging toxicology study, based on differences in manufacturing processes there is a need to qualify the impurity profile of your pitavastatin magnesium drug substance versus the listed drug Livalo, which you plan to reference. A comparison between an unapproved pitavastatin calcium substance and your pitavastatin magnesium substance is not acceptable for a 505(b)(2) application. The listed drug needs to be a US approved product. We recommend that you submit the protocol for your proposed comparative bridging toxicology study to the Agency prior to its initiation, in order to ensure adequacy. Potentially genotoxic impurities and degradation products may necessitate additional nonclinical qualification per ICH-Q3A and ICH-Q3B.

In the current submission, one-month toxicity study is provided with their drug product and Livalo, but no gene-toxicities are provided.

### 2.6.2 PHARMACOLOGY

Pitavastatin is an HMG-CoA reductase inhibitor (statin). Pitavastatin calcium is currently marketed by Kowa Co., LTD, under NDA 022363 (Livalo).

Pitavastatin is a potent statin, with an $IC_{50}$ for HMG-CoA of 6.8 nM. While pitavastatin is not known to lower serum cholesterol in any strain of rats (similar to other statins), it does lower serum cholesterol in mice, guinea pigs, rabbits, dogs, and monkeys. Pitavastatin was also active *in vitro* in human HepG2 cell cultures.

Zydus pharmaceutical's each film-coated tablet of pitavastatin contains 1.026 mg, 2.053 mg, or 4.106 mg of pitavastatin magnesium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base and the following inactive ingredients: calcium carbonate, crospovidone, hypromellose, lactose monohydrate, magnesium stearate and sodium carbonate anhydrous and film- coating containing the following inactive ingredients: hypromellose, polyethylene glycol, talc and titanium dioxide

Pitavastatin Magnesium exhibits isomerism. It is (3R, 5S) isomer; it has two chiral centers and hence has four stereoisomers including Pitavastatin Magnesium. The drug is manufactured in the (b) (4) form (see DMF (b) (4)

Zydus Pharmaceuticals (USA) Inc. has stated that Cadila Healthcare Limited, Dabhasa, India is the provider of the active pharmaceutical Ingredient (API), i.e. Pitavastatin Magnesium.

The following Table describes the composition of the proposed drug to the reference drug (Livalo).

### 1.12.12 Comparison between Generic Drug and Reference Listed Drug

This section identifies the following information for comparing the proposed drug with that of the reference-listed drug:

| Title | Reference Listed Drug [Livalo® (pitavastain calcium) Tablets], Application Holder: Kowa Pharmaceuticals America] | Proposed Drug Product [Pitavastatin (Magnesium Salt) Tablets], Application Holder: Zydus Pharmaceuticals (USA) Inc.] |
|---|---|---|
| **Condition of Use** | Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) | Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) |
| **Active Ingredient(s)** | Pitavastain Calcium | Pitavastain Magnesium |
| **Inactive Ingredient(s)** | Lactose monohydrate<br>Low substituted hydroxypropyl cellulose<br>Hypromellose<br>Magnesium aluminometasilicate<br>Magnesium stearate<br><br>***Coating Contains***<br>Hypromellose<br>Titanium Dioxide<br>Triethyl citrate<br>Colloidal anhydrous silica | Lactose Monohydrate, NF<br>Crospovidone, NF<br>Hypromellose, USP<br>Sodium Carbonate, NF<br>Calcium Carbonate, NF<br>Magnesium Stearate, NF<br><br>***Coating Contains***<br>(b) (4)<br>(Hypromellose USP, Titanium Dioxide USP, PEG, (b) (4) (b) (4) and Talc, USP)<br>(b) (4) |
| **Route of Administration** | Oral | Oral |
| **Dosage Form** | Tablets | Tablets |
| **Strength(s)** | 1 mg 2 mg and 4 mg | 1 mg 2 mg and 4 mg |
| **Bio-Strength (Strength on which in-vivo bio-equivalence study have been performed)** | 4 mg | 4 mg |

*Does not remain in final product, except in traces.

## Impurities (Pitavastatin Magnesium)

Sponsor states that Pitavastatin Magnesium is non-compendial drug substance. As per the information provided in DMF, following impurities are shown in Pitavastatin Magnesium: Maximum daily dose is 4 mg/day.

**Drug substance impurities**: Listing of potential impurities in the drug substance are provided below:

**Listing of Potential Impurities:**

(b) (4)

(b) (4)

The total drug intake and proposed acceptance criteria for specification of impurities in the drug substance are provided below:

(b) (4)

Note that the drug impurities present in the drug substance fall within the proposed limits, as stated below:

Batch analysis of the drug substance (AR No. 0908035082, 0908035083 and 0908035084) indicated that impurities levels fall well within the proposed limits. Chromatograms of test samples and the reference standard are located in **Module 3.2.S.4.3** (AR No. 0908035082, 0908035083 and 0908035084).

| Impurity Name | Results (API Lots) | | | Proposed Acceptance criteria |
|---|---|---|---|---|
| | 0908035082 | 0908035083 | 0908035084 | |
| (b) (4) | Not detected | BQL | Not detected | NMT (b) (4) % |
| | (b) (4) | Not detected | Not detected | NMT % |
| | BQL | BQL | BQL | NMT % |
| | BQL | BQL | BQL | NMT % |
| | BQL | BQL | BQL | NMT % |
| | BQL | Not detected | BQL | NMT % |
| | Not detected | Not detected | Not detected | NMT % |
| | BQL | BQL | BQL | NMT % |
| Total impurities | (b) (4) | 0.00% | 0.00% | NMT % |

**Drug product impurities**:

***Characterization of Impurities in the drug product***

*Based on chemistry, forced degradation data of drug substance and product development studies, specified identified impurities* (b) (4) *have been controlled in the drug product during release and stability testing. All process related impurities of drug substance are not included in the finished product specification; however, existing method is capable to detect all process impurities.*

*For a more detailed discussion on characterization of impurities and their control in the drug substance, please refer to* ***Module 3.2.S.3.2*** *in Type II DMF (DMF#* (b) (4) *of Pitavastatin Magnesium submitted by Cadila Healthcare Limited, Dabhasa, India.*

Table. Potential degradation products of Pitavastatin magnesium are listed below:

**Listing of Potential Degradation Products**

(b) (4)

[redacted]

To establish a "bridge" between proposed drug product (i.e Pitavastatin (Magnesium Salt) and reference drug (i.e LIVALO), the sponsor has conducted following non clinical study:

Four-week Repeated Dose Toxicity Study of Pitavastatin Tablets (Magnesium Salt, drug lot # EMN268) by Oral Route in Wistar Rats with 2 - Weeks Recovery Period to the toxicity with the reference drug, LIVALO (Pitavastatin calcium).

## 2.6.6 TOXICOLOGY

### 2.6.6.3 Repeat Dose Toxicity Studies

In the current application, sponsor has submitted a 4-week toxicity study with a 2-week recovery period. We requested a clean copy of the final report of the above study as well as the summary of histopathology findings, which were provided in the submission #0002 (7/6/2015). The submitted toxicity study is reviewed below.

**4-Weeks Toxicity Study Of Pitavastatin Tablets 4 Mg (Magnesium Salt) By Oral Route In Wistar Rats With 2- Weeks Recovery Period.**

**Study no.**: 410-1-02-8743
**Volume #, and page #**: eCTD submission on 7/6/2015.
**Sponsor:** Cadila Healthcare Limited, Moraiya, Ahmedabad, Gujarat, India.

**Conducting laboratory and location**: (b) (4)

**Date of study initiation**: 11/13/2014
**GLP compliance**: Yes
**QA report**: yes (X ) no ( ).

**Drug, lot #, and % purity**: Drug lot # EMN268 (manufactured in March, 2013 (appendix 18 / purity was 102.8 %. see below:

The details of the test item provided by the Sponsor are as follows:

| | |
|---|---|
| Test Item Name | Pitavastatin Tablets 4 mg (Magnesium salt) |
| IUPAC Name | Information not provided by the Sponsor |
| CAS Number | Information not provided by the Sponsor |
| Batch/Lot Number | EMN268 |
| Analyzed Purity | (b) (4) % of stated amount)<br>(Refer the Certificate of Analysis in APPENDIX 18) |
| Manufactured by | Cadila Healthcare Ltd., India |
| Supplied to (b) (4) by | Cadila Healthcare Ltd., India |
| Date of Manufacture | March 2013 |
| Retest date | (b) (4) |

The details on the reference drug Livalo are shown below:

**Reference Item**

The details of the reference item provided by the Sponsor are as follows:

| | |
|---|---|
| Reference Item Name | LIVALO® (Pitavastatin) Tablets 4 mg |
| IUPAC Name | Information not provided by the Sponsor |
| CAS Number | Information not provided by the Sponsor |
| Batch/Lot Number | 3113878 |
| Analyzed Purity | (b) (4)<br>(Refer the Certificate of Analysis in APPENDIX 18) |
| Manufactured by | Patheon, Inc. Cincinnati, OH 45237 USA or by Kowa Company Ltd., Nagoya 462-0024, Japan |

| | |
|---|---|
| Supplied to (b) (4) by | Cadila Healthcare Ltd., India |
| Date of Manufacture | Information not provided by the Sponsor |
| Date of Expiry | July 2016 |

**Formulation/vehicle**:

**Placebo**

The details of the placebo provided by the Sponsor are as follows:

| | |
|---|---|
| Name | Placebo Tablet of Pitavastatin Tablet 4 mg (Magnesium salt) |
| Batch/Lot Number | (b) (4)239 |
| Manufactured by | Cadila Healthcare Ltd., India. |
| Supplied to (b) (4) by | Cadila Healthcare Ltd., India. |
| Analyzed Purity | 0.0% (Refer the Certificate of Analysis in APPENDIX 18) |
| Date of Manufacture | June 2014 |
| Date of Expiry | May 2015 |
| Appearance | White to off white, beveled edge, round shaped tablets debossed with "878" on one side and plain on other side. The tablet is free of all physical defects |
| **Storage Condition (at** (b) (4) | As per the instruction received from the Sponsor on storage of the placebo, the placebo was stored :<br>Storage Temperature: Room temperature between (b) (4)<br>Other Specifications: Protect from light<br>Storage Container: In original container as supplied by the Sponsor<br>Storage Location : Test Item Control Office, (b) (4) |

**Methods (unique aspects):**

**Species**: Healthy, Wistar strain rats were obtained from (b) (4). At the initiation of dosing, they were 7-9 weeks of age.

**Diet and water**: The animals were fed *ad libitum* with standard pellet diet (Teklad Certified Global 16% Protein Rodent diet, from (b) (4) with unlimited filtered drinking water.

**Doses in administered units:** 0 (vehicle), 0 (crushed placebo tablets), 2, 5, 10 mg/kg/day of the current drug (crushed Pitavastatin magnesium tablets) and the reference drug Livalo (crushed Livalo tablets) at doses of 2, 5, 10 mg/kg/day) were administered to Wistar rats (10/sex/group) for 4 weeks, followed by a 2 week of the drug free recovery period. Doses were administered once daily by oral gavage. The dose volume was 10 mL/kg was used. The vehicle control rats were administered with the vehicle only, and there was also a placebo group included in the study design as shown below.

A study design is shown below:

**6.8 Experimental Outline**

| Group N° | Group | Dose (mg/kg b. wt) | N° of Animals | | Animal ID N° | | Cage N° | |
|---|---|---|---|---|---|---|---|---|
| | | | M | F | M | F | M | F |
| **Main Groups** | | | | | | | | |
| G1 | Vehicle Control | 0 | 10 | 10 | 1-10 | 11-20 | 1-5 | 6-10 |
| G2 | Placebo Tablet of Pitavastatin Tablet 4 mg (Magnesium salt) | 0 | 10 | 10 | 21-30 | 31-40 | 11-15 | 16-20 |
| G3 | Pitavastatin Tablet 4 mg (Magnesium salt)-Low Dose | 2 | 10 | 10 | 41-50 | 51-60 | 21-25 | 26-30 |
| G4 | Pitavastatin Tablet 4 mg (Magnesium salt)-Mid Dose | 5 | 10 | 10 | 61-70 | 71-80 | 31-35 | 36-40 |
| G5 | Pitavastatin Tablet 4 mg (Magnesium salt)-High Dose | 10 | 10 | 10 | 81-90 | 91-100 | 41-45 | 46-50 |
| G6 | LIVALO® (Pitavastatin) tablets 4 mg-Low Dose | 2 | 10 | 10 | 101-110 | 111-120 | 51-55 | 56-60 |
| G7 | LIVALO® (Pitavastatin) tablets 4 mg -Mid Dose | 5 | 10 | 10 | 121-130 | 131-140 | 61-65 | 66-70 |
| G8 | LIVALO® (Pitavastatin) tablets 4 mg -High Dose | 10 | 10 | 10 | 141-150 | 151-160 | 71-75 | 76-80 |
| **Recovery Groups** | | | | | | | | |
| G9 | Placebo Tablet of Pitavastatin Tablet 4 mg (Magnesium salt) Recovery | 0 | 10 | 10 | 161-170 | 171-180 | 81-85 | 86-90 |
| G10 | Pitavastatin Tablet 4 mg (Magnesium salt)-High Dose Recovery | 10 | 10 | 10 | 181-190 | 191-200 | 91-95 | 96-100 |
| G11 | LIVALO® (Pitavastatin) tablets 4 mg-High Dose Recovery | 10 | 10 | 10 | 201-210 | 211-220 | 101-105 | 106-110 |
| **TK Groups** | | | | | | | | |
| G12 | Placebo Tablet of Pitavastatin Tablet 4 mg (Magnesium salt) | 0 | 10 | 10 | 221-230 | 231-240 | 111-115 | 116-120 |
| G13 | Pitavastatin Tablet 4 mg (Magnesium salt)-Low Dose | 2 | 10 | 10 | 241-250 | 251-260 | 121-125 | 126-130 |
| G14 | Pitavastatin Tablet 4 mg (Magnesium salt)-Mid Dose | 5 | 10 | 10 | 261-270 | 271-280 | 131-135 | 136-140 |
| G15 | Pitavastatin Tablet 4 mg (Magnesium salt)-High Dose | 10 | 10 | 10 | 281-290 | 291-300 | 141-145 | 146-150 |
| G16 | LIVALO® (Pitavastatin) tablets 4 mg-Low Dose | 2 | 10 | 10 | 301-310 | 311-320 | 151-155 | 156-160 |
| G17 | LIVALO® (Pitavastatin) tablets 4 mg -Mid Dose | 5 | 10 | 10 | 321-330 | 331-340 | 161-165 | 166-170 |
| G18 | LIVALO® (Pitavastatin) tablets 4 mg-High Dose | 10 | 10 | 10 | 341-350 | 351-360 | 171-175 | 176-180 |

**Dose Justification**: The doses were selected based on results of a 4 week toxicity study conducted with Pitavastatin Calcium and Pitavastatin Magnesium performed ((b) (4) Study N° 410-1-02-7084). Sponsor states that *Livalo NDA report indicated that the dose levels of 50 and 100 mg/kg/day were associated with adverse effects; mild effects were observed at a dose 10 mg/kg./day.*

**Following parameters were evaluated:**

Each rat was observed twice daily for visible signs of reaction to treatment, morbidity and mortality during treatment and recovery periods. Body weight and food consumption were determined at weekly interval. Ophthalmological examination was made on all animals from each group (except in TK groups) prior to the initiation of treatment and prior to terminal (G1, G2, G5 and G8) and recovery periods (G9 to G11). Hematological and biochemical analyses were performed at the end of the treatment (G1 to G8) and the recovery periods (G9 to 11). Urine samples were collected from all animals at the end of the treatment (G1 to G8) and the recovery period (G9 to G11).

*Neurobehavioral observation (NBO) tests were performed on all animals prior to the initiation of treatment (G1 to G8) and weekly thereafter. Functional Observation Battery (FOB) was performed during 4th week of treatment (G1 to G8) and 2nd week of recovery period (G9 to G11). The details on NBO are described below:*

**7.5 Neurobehavioural Observation (NBO)**

To assess the behavioral and neurological status of each animal, the following parameters of NBO were evaluated in all animals prior to initiation of treatment and at weekly intervals.

**7.5.1 Home Cage Observations**

In home cage, the animals were observed for posture and presence or absence of convulsions.

**7.5.1.1 Posture**

The posture of the animal was observed in the home cage upon initial approach by the observer and description of the posture was recorded as

- Flattened, limbs may be spread out
- Lying on side
- Curled up often asleep
- Sitting but with head hung down (Sitting A)
- Sitting normally, feet tucked in (Sitting B)
- Sitting or standing alert, watching (Sitting C)
- Rearing

- Vertical jumping
- Writhing
- Circling

**7.5.1.2 Convulsions**

In the home cage, animals were also observed for presence or absence of convulsions (clonic and tonic movements).

**7.5.2 Observations during Removal and Handling**

After completing home cage observations, the rat was picked up by the observer and observed for the ease of removal from the home cage, handling reactivity of the animal, eye abnormalities, skin abnormalities and autonomic signs such as palpebral closure, lacrimation, salivation and piloerection.

**7.5.2.1 Ease of Removing Rat from Cage**

The reactivity of the animal to being removed from its home cage was ranked based on the intensity of its reaction as very easy, easy, moderately difficult, difficult or very difficult.

**7.5.2.2 Handling Reactivity**

A subjective measurement of the reaction of the animal while being held by the observer was rated as very easy, easy, moderately easy, freezes or difficult.

**7.5.2.3 Palpebral Closure**

The degree of closure of the eyelids during the time when the animal was held by the observer was ranked as eyelids wide open, slightly closed, ptosis or eyelids completely closed.

**7.5.2.4 Lacrimation**

The degree of lacrimation was rated and recorded as none, slight or severe.

**7.5.2.5 Eye Examination**

Eyes were examined for presence or absence of exophthalmus, microphthalmus, opacity, cataract, chemosis, conjunctivitis, discharge and others abnormalities, if any.

**7.5.2.6 Piloerection**

Piloerection was differentiated from a scruffy or ungroomed coat by patting the back of the animal in a rostral to caudal direction. When the animal's hair erected even after patting that was considered as piloerection. The presence or absence of piloerection was recorded.

**7.5.2.7 Skin Examination**

Animal's skin was examined for abnormalities such as rough coat, alopecia and dermatitis etc.

**7.5.2.8 Salivation**

The degree of salivation was rated as none, slight or severe.

#### 7.5.3 Open Field Measurements

For open field observations, rats were placed (one at a time) in an open arena (size: 495 mm x 495 mm x 203 mm) with a flat surface covered with clean absorbent paper on it and observed for a period of 3 minutes. Fresh absorbent paper was placed for each animal. During the 3 minute period, the following observations were made and recorded.

##### 7.5.3.1 Gait

The walking pattern of the rat was evaluated by observing movements of the rat in the open field box during 3 minutes test period. The observations were ranked in terms of severity as normal, slightly abnormal or severely abnormal.

##### 7.5.3.2 Mobility Score

A measure of the ability of the animal to locomotor despite gait abnormalities was recorded. The ranking of the degree of impairment of locomotion was recorded as normal, slightly impaired or totally impaired.

##### 7.5.3.3 Arousal Level

A ranking of the level of unprovoked activity and alertness of the animal in the open field was recorded during the 3 minutes observation period. Observations on arousal were ranked as very low, low, high or very high.

##### 7.5.3.4 Vocalizations

The actual number of spontaneous or unprovoked vocalizations was recorded.

##### 7.5.3.5 Rearing

The number of times the rat raises its front paws off the floor is considered rearing. The number of these actions was counted for the 3 minutes observation period and the total number of rearing was recorded.

##### 7.5.3.6 Respiration

Any apparent alteration in the rate and/or ease of respiration was recorded as normal, dyspnoea, abdominal breathing, gasping, snuffles or tachypnoea.

##### 7.5.3.7 Clonic or Tonic Movements

In the open field, each animal was observed for presence or absence of clonic or tonic movements. The observations for clonic movement were recorded as chewing (clonus of the jaws), mild clonic tremors of limbs and repetitive clonic tremors of the whole body or absent. Tonic movements were recorded as tonic contraction of hind limb, opisthotonos - backward, emprosthotonos - forward or absent.

##### 7.5.3.8 Urination and Defecation

Actual number of urine pools and fecal boluses at the end of 3-minute observation period was recorded.

#### 7.6.1.5 Pupil Response

The beam of a pocket-sized flashlight was brought from a lateral position medially towards the center of the face of the animal. Constriction of the pupil was observed as a positive response. The degree of elicited response was recorded as normal or abnormal.

#### 7.6.1.6 Air Righting Reflex

The animal was held supine, with the hands of the observer under the back and shoulders of the animal for support. The animal was dropped from a height of approximately 30 cm. The ease and uprightness of the landing was recorded as normal, slightly abnormal, moderately abnormal or severely abnormal.

#### 7.6.1.7 Landing Hind limb Foot Splay

The Hind limb foots of each rat was marked with a non-permanent, non-toxic ink just prior to testing. The animal was suspended in a prone position and then dropped from a height of approximately 30 cm on to a recording sheet. This procedure was repeated three times. The distance between two foot prints was measured and average of the three foot splay values was calculated.

### 7.6.2 Grip Strength

Grip strength of both forelimb and hindlimb were measured during the 4$^{th}$ week of treatment period and during 2 $^{nd}$ week of recovery period with a grip strength meter (Columbus Instruments, Ohio, USA) to determine the ability of the animal to grasp and hold on the mesh platform. The grip strength of each animal was measured for 3 consecutive times; the results were averaged separately for the forelimb and hindlimb.

### 7.6.3 Motor Activity

Motor activity of each animal was monitored during the 4$^{th}$ week of treatment period and during 2 $^{nd}$ week of recovery period using an automated Photobeam Activity system (San Diego Instrument Inc., San Diego) equipped with a computer analyser. Animals were monitored for three consecutive 10 minutes intervals allowing for examination of both exploratory and acclimation activity levels. During this period, total and ambulatory activity of the animal was evaluated. The following motor activity parameters were reported and used for comparisons: Total activity, Ambulatory activity and Fine activity.

## 7.7 Ophthalmological Examination

A complete ophthalmological examination was performed on each rat with the aid of ophthalmoscope. Ophthalmic examination was performed on all rats once before commencement of treatment and at terminal sacrifice; ophthalmological examination was performed first in the vehicle control, placebo and high dose groups. As no treatment related effect was observed in opthalmological examination of high dose groups animals hence, opthalmological examination of low and mid dose group was not performed.

Additionally animals from the recovery group were observed at the end of recovery periods. In order to facilitate easy examination of the interior part of the eye, homatropine (2%) eye drops was used as a dilatant to dilate the pupil. This mydriatic solution was instilled into the eye 20 minutes before the eye examination.

**Gross pathology:** Main study animals were sacrifice on day 29, recovery animals on day 43.

**Organs weighed**: Samples of tissues and organs were collected and weighed (as stated below under histopathology). Prepared bone marrow smears were not evaluated, as no abnormality was found in hematology parameters.

**Histopathology:** This was performed at sacrifice in controls (vehicle and placebo group) and high dosed animals only (Pitavastatin magnesium, and the comparator Livalo) in organs as stated below.

*Histopathological examination was carried out for organs and tissues from the vehicle control (G1), placebo control (G2), test item high dose group (G5) and reference item high dose group (G8). In addition all gross lesions were subjected to histopathological examination.*
*Severity grade of lesions were recorded as minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+).*

*Histopathological observation and peer review were extended to lower dose groups (G3, G4, G6 and G7) and recovery groups (G9, G10 and G11) for treatment related effect in stomach.*

*Peer review of histopathology slides was performed by the reviewing pathologist as per the standard operating procedure (APPENDIX 13).*

**APPENDIX 13 (Continued)**

| Tissue | Weight | Fix |
|---|---|---|
| Adrenal glands | X | X |
| Aorta | – | X |
| Bone marrow smear from femur* | – | X |
| Bone with bone marrow (femur bone with articular cartilage) | – | X |
| Brain – cerebrum, cerebellum, midbrain | X | X |
| Cecum | – | X |
| Colon | – | X |
| Duodenum | – | X |
| Epididymides | X | X |
| Oesophagus | – | X |
| Eyes with optic nerve | – | X |
| Gross lesions if any | – | X |
| Harderian gland | – | X |
| Heart | X | X |
| Ileum with Peyer's pathches | – | X |
| Jejunum | – | X |
| Kidneys | X | X |
| Liver | X | X |
| Lung including main bronchi | X | X |
| Mammary glands | – | X |
| Lymph nodes – mesenteric, iliac and prescapular | – | X |
| Ovaries | X | X |
| Pancreas | – | X |
| Sciatic nerve | – | X |
| Pituitary | – | X |
| Prostate | – | X |
| Rectum | – | X |
| Salivary glands | – | X |
| Seminal vesicle with coagulation gland | – | X |
| Skeletal muscle | – | X |
| Skin | – | X |
| Spinal cord at three levels cervical, mid thoracic and lumbar | – | X |
| Spleen | X | X |
| Stomach | – | X |
| Testes | X | X |
| Thymus | X | X |
| Thyroid with parathyroid | – | X |
| Trachea | – | X |
| Urinary bladder | – | X |
| Uterus with cervix | X | X |
| Vagina | – | X |

**Toxicokinetic (TK) analysis**: Toxicokinetics assessment of test and reference drug was performed on the satellite animals using a sparse sampling design. Blood samples were collected at 0, 0.5, 1, 2, 4, 8, 12 and 24 hours post dose on days 1 and 28.

The pitavastatin drug levels in the rat plasma were measured using a high performance liquid chromatography with tandem mass spectrometry method (LC-MS/MS) at Zydus Research Centre, Ahmedabad, India.

**Results:**

**Dose formulation analysis**:
The results show homogeneity of Pitavastatin and Livalo in the formulation used.

The results of A.I. and homogeneity of dose formulation samples collected on days 1 and 28 for low, mid and high dose are as below:

| Interval of Sample Collection | Concentration (mg/mL) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pitavastatin Tablet 4 mg (Magnesium salt) | | | | | | LIVALO® (Pitavastatin) tablets 4 mg | | | | | |
| | 0.2 | | 0.5 | | 1.0 | | 0.2 | | 0.5 | | 1.0 | |
| | % Mean Recovery | % RSD | % Mean Recovery | % RSD | % Mean Recovery | % RSD | % Mean Recovery | % RSD | % Mean Recovery | % RSD | % Mean Recovery | % RSD |
| Day 1 | 102.08 | 0.31 | 107.61 | 0.09 | 100.84 | 0.41 | 95.71 | 0.64 | 92.48 | 0.18 | 91.30 | 0.13 |
| Day 28 | 99.81 | 0.18 | 99.73 | 0.52 | 99.56 | 0.30 | 107.46 | 0.18 | 107.50 | 0.06 | 104.34 | 0.28 |

The homogeneity and active ingredient content of Pitavastatin Tablet 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) tablets 4 mg in RO water was within the acceptable range of the target concentration ± 10% (APPENDIX 12).

Following certificates of analysis (CAO) were provided in the appendix-18 for the two drug products, used in the 28-day toxicity study in rats.

**Certificate of analysis (COA) for Pitavastatin**

Table 1. Certificate of analysis for the current drug product. Note that Pitavastatin magnesium contains (b) (4) impurity and total degradation products in the drug product are shown to be (b) (4).

**CERTIFICATE OF ANALYSIS**

| | | | |
|---|---|---|---|
| Name of Product | **PITAVASTATIN TABLETS 4 mg (Magnesium salt)** | | |
| Batch No. | EMN268 | | |
| Mfg. Date | 03/2013 | Retest Date | (b) (4) |
| Date of Report | 05/11/2014 | Manufactured by | Cadila Healthcare Ltd., Moraiya, India |

RESULTS OF ANALYSIS

| **Tests** | **Results** |
|---|---|
| **Description** | White, beveled edge, round shaped tablets debossed with "878" on one side and plain on the other side. The tablet is free of all physical defects. |
| **Identification (By HPLC)** | In the assay, the retention time of the principal peak in the chromatogram obtained with the sample preparation is the same as that of the principal peak obtained with the standard preparation. |
| (b) (4) | (b) (4) |
| **Uniformity of dosage units (by content uniformity).** | Acceptance value: (b) (4) |
| **Related substances(By HPLC):** (b) (4)<br>**Any individual unknown degradation products**<br>**Total degradation products** | (b) (4)<br>Not detected<br>Not detected<br>(b) (4) |
| **Assay(By HPLC) :**<br>**Each tablet contains:**<br>**Pitavastatin Magnesium equivalent to Pitavastatin.** | (b) (4) |

Table 2. Certificate of analysis for the reference drug product (Livalo). No degradation products/impurities are provided in the reference drug Livalo here.

**Certificate of analysis (COA) for Livalo**

**CERTIFICATE OF ANALYSIS**

Name of Product **Livalo® (Pitavastatin) Tablets 4 mg**

Batch No. 3113878

Exp. Date 07/2016

Date of Report 03/11/2014

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

RESULTS OF ANALYSIS

| Tests | Results |
|---|---|
| **Description** | Round white film-coated tablet debossed "KC" on one face and "4" on the reverse. |
| **Identification (By HPLC)** | In the assay, the retention time of the principal peak in the chromatogram obtained with the sample preparation is the same as that of the principal peak obtained with the standard preparation |
| [redacted] | (b) (4) |
| **Uniformity of dosage units (by content uniformity).** | Acceptance value: (b) (4) |
| **Assay(By HPLC) : Each tablet contains: Pitavastatin Calcium equivalent to Pitavastatin.** | (b) (4) |

**Mortality:** No treatment related mortality was observed.

**Clinical signs:** These were unremarkable (these were described as the number of normal animals during week).

**Body weights:** At a HD of Pitavastatin magnesium (group G10), i.e. the recovery group male rats showed statistically significant decrease in percent body weight change during week PT-1 when compared with placebo control recovery group (G9); these were13.7* vs 16.6 g in the control group, *p<0.05, see Table below. However, note that this difference may not be biologically significant.

The mean body weight and percent body weight change of animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg were comparable to placebo control groups except statistically significant decrease in percent body weight change during week PT-1 was observed in male rats of Pitavastatin Tablets 4 mg (Magnesium salt) high dose recovery group (G10) when compared with placebo control recovery group (G9).

These changes could be considered as incidental findings as only intermittently occurred and not observed in other treatment groups. Overall mean body weight and body weight change between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable (TABLE 11, TABLE 12; APPENDIX 9 and APPENDIX 10).

**Groups were designated as shown below**:

**Main animals** treatment groups

| | |
|---|---|
| Vehicle and Placebo Controls: | G1, G2 |
| Pitavastatin magnesium (LD, MD, HD) | G3, G4, G5 |
| Livalo (pitavastatin calcium (LD, MD, HD) | G6, G7, G8 |
| **Recovery**-(Placebo, HD Pitavastatin, HD Livalo) | G9, G10, G11 |

Table. Recovery animals-Group mean body weight changes (males and females) in grams (g) at a HD of 10 mg/kg/day

**Dose: G9-0; G10-10; G11-10 mg/kg b. wt./day** **Sex: Male**

| Week | G9 (N = 10) | | G10 (N = 10) | | G11 (N = 10) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| PT - 1 | 16.55 | 1.85 | 13.72↓** | 2.44 | 14.95 | 1.81 |
| PT - 2 | 30.15 | 3.47 | 26.61 | 5.23 | 28.22 | 2.76 |
| PT - 3 | 40.54 | 4.88 | 36.69 | 6.45 | 37.94 | 4.65 |
| PT - 4 | 47.84 | 5.23 | 43.70 | 7.01 | 46.96 | 5.85 |
| PT - 5 | 58.16 | 5.57 | 52.29 | 6.91 | 55.07 | 6.52 |
| PT - 6 | 63.21 | 5.42 | 57.21 | 7.85 | 59.04 | 7.33 |

**Sex: Female**

| Week | G9 (N = 10) | | G10 (N = 10) | | G11 (N = 10) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| PT - 1 | 8.34 | 2.78 | 10.36 | 5.03 | 8.49 | 2.88 |
| PT - 2 | 17.86 | 2.23 | 18.40 | 4.87 | 16.38 | 3.86 |
| PT - 3 | 23.63 | 4.87 | 24.46 | 4.75 | 22.98 | 2.70 |
| PT - 4 | 29.63 | 3.19 | 30.19 | 4.84 | 29.45 | 3.42 |
| PT - 5 | 36.46 | 3.95 | 36.89 | 6.21 | 34.30 | 5.08 |
| PT - 6 | 37.95 | 3.47 | 38.39 | 8.09 | 38.23 | 4.31 |

**Food consumption**: No effects on food consumption were noted. Food consumption (FC) was comparable between Pitavastatin magnesium and Livalo groups

**Ophthalmoscopy:** No drug related effects were observed on ophthalmological parameters. Note that these were performed in controls and at a HD only, in both Pitavastatin magnesium and Livalo groups.

**Neuro-behavioral observations**: No effects on Neuro-behavioral observations were noted. The methods are described below:

*The neurobehavioral observations conducted weekly in home cage, during handling and in open field did not reveal any abnormality across all the groups. During home cage observation, normal posture was observed in all animals from treated groups (G3 to G8 and G10 to G11) as well as control (G1, G2 and G9) groups. All animals revealed normal postures viz., asleep (curled up often asleep), sitting A (sitting but with head hung down), sitting C (sitting or standing alert, watching) or rearing in home cage. Clonic and tonic movements were not observed in home cage during weekly neurobehavioral observations.*

*Neurobehavioral observations made during removal and handling of animals did not reveal any*

*abnormalities related to treatment. None of animals showed lacrimation and salivation. Eyelids were wide open in all rats. Piloerection was absent in all animals. Eye and skin examination revealed no treatment related abnormality.*

*In open field, all animals from the control and the treatment groups showed normal gait and mobility during 3-minutes observation period. No treatment related changes were observed in rearing, urination and defecation count in male as well as female rats of treated groups (G3 to G8 and G10 to G11) when compared with the placebo control groups (G2 and G9) respectively.*

*Respiration was normal in all the animals. The clonic or tonic movements, vocalization, stereotypy and bizarre behavior were absent in across all the groups. All the neurobehavioural parameters between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg were comparable (table 4, table 5, table 6; appendix 4).*

**Functional Observational Battery (FOB)**

**Sensory Reactivity Observations**
*Sensory reactivity parameters viz., approach response, touch response, click response, tail pinch response, pupil response and air righting reflex in animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg were comparable to placebo control groups. Sensory reactivity parameters viz., approach response, touch response, click response, tail pinch response, pupil response and air righting reflex between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg were comparable (TABLE 7; APPENDIX 5).*

**Hind-limb Foot Splay**: In males, decreased hindlimb foot splay was noted at a HD of Zydus's Pitavastatin magnesium and at MD of Livalo vs controls (71.7*, 64.4* vs 89.3 mm, *p<0.05). At the end of the drug free recovery period, the decreased hindlimb foot splay was still noted with a HD of Zydus's Pitavastatin magnesium but not with Livalo (62.8** vs 76.5 mm, **p<0.01).

Hindlimb foot splay value in animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable to placebo control groups except statistically significant decrease in hindlimb foot splay value was observed in male rats of Pitavastatin Tablets 4 mg (Magnesium salt) high dose (G5), high dose recovery (G10) and LIVALO® (Pitavastatin) Tablets 4 mg mid dose (G7) groups when compared with respective placebo control groups (G2 and G9). These changes were not associated with any other muscular activity hence it could not be considered as toxicological relevance. Overall value of Hindlimb foot splay between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable (TABLE 8; APPENDIX 6).

Groups were designated as shown below:

| | |
|---|---|
| Main study animal groups | |
| Vehicle and Placebo Controls: | G1, G2 |
| Pitavastatin magnesium (LD, MD, HD) | G3, G4, G5 |
| Livalo (pitavastatin calcium (LD, MD, HD) | G6, G7, G8 |
| Recovery animals- (Placebo, HD Pitavastatin, HD Livalo) | G9, G10, G11 |

Table. The hindlimb foot splay findings with Pitavastatin magnesium and Livalo

**TABLE 8: Hindlimb Foot Splay Record (mm) - Group Mean Values**

**Dose: G1-0; G2-0; G3-2; G4-5; G5-10; G6-2; G7-5; G8-10; G9-0; G10-10; G11-10 mg/kg b. wt./day**

| Hindlimb Foot Splay | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Sex** | | **G1** | **G2** | **G3** | **G4** | **G5** | **G6** | **G7** | **G8** |
| Male (N = 10) | **Mean** | 89.3 | 92.9 | 77.0 | 82.5 | 71.7↓* | 76.2 | 64.6↓* | 73.0 |
| | **SD** | 20.8 | 19.6 | 15.4 | 19.6 | 24.1 | 9.6 | 13.1 | 13.9 |
| Female (N = 10) | **Mean** | 66.1 | 69.7 | 70.9 | 69.5 | 66.7 | 77.2 | 63.1 | 61.2 |
| | **SD** | 15.8 | 14.5 | 13.4 | 23.1 | 20.9 | 27.2 | 13.4 | 13.4 |

| Hindlimb Foot Splay | | | | |
|---|---|---|---|---|
| **Sex** | | **G9** | **G10** | **G11** |
| Male (N = 10) | **Mean** | 76.9 | 62.8↓** | 76.5 |
| | **SD** | 11.1 | 7.9 | 16.5 |
| Female (N = 10) | **Mean** | 67.7 | 73.4 | 76.6 |
| | **SD** | 13.5 | 17.1 | 13.0 |

**Motor Activity and Grip strength**: No significant findings were noted in the motor activity or grip strength, see below:

The motor activity data of animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable to placebo control groups. Statistically significant decrease in fine activity at interval 11-20 minutes was observed in male rats of placebo control group (G2) when compared with vehicle control group (G1). These changes could be considered as incidental findings as only intermittently occurred and not observed in other treatment groups. The motor activity data between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable (TABLE 9; APPENDIX 7).

**Grip Strength**

The forelimb and hindlimb grip strength of animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable to placebo control groups. The forelimb and hindlimb grip strength data between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable (TABLE 10; APPENDIX 8).

**Hematology:** No treatment related changes in hematological parameters were noted with Pitavastatin magnesium or LIVALO when compared to placebo control groups. Overall hematological data between animals treated with Pitavastatin magnesium and LIVALO® was comparable (APPENDIX 13).

**Clinical chemistry**: Statistically significant increase in serum LDL was observed in male rats with LIVALO at a HD of 4 mg (G8 vs placebo control G2 group).

| Parameter | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
|---|---|---|---|---|---|---|---|---|
| LDL – Male | 7.47 | 8.10 | 8.30 | 9.77 | 9.51 | 8.21 | 8.79 | 10.59↑ |
| LDL - Female | 6.70 | 6.50 | 7.12 | 7.23 | 7.53 | 6.94 | 7.91 | 7.54 |
| ALT - Female | 29.07 | 28.12 | 29.50 | 32.92 | 31.53 | 29.12 | 32.92↑ | 32.74 |
| T.PRO - Female | 6.77 | 6.50 | 6.82 | 6.83 | 7.03↑ | 6.97↑ | 6.83 | 6.88 |
| CHO - Female | 48.13 | 43.78 | 56.28 | 57.70↑ | 57.56 | 49.43 | 56.52 | 53.78↑ |
| ALP - Female | 64.51 | 81.13 | 55.87↓ | 68.64 | 60.64↓ | 60.49↓ | 59.18↓ | 65.22 |

**Urinalysis**: No effects were noted in urinalysis in animals with Pitavastatin magnesium or Livalo (APPENDIX 13).

**Gross pathology**: No effects on gross pathology were noted, except in epididymides, see below.

Visceral examination of the terminally sacrificed animals revealed multifocal, unilateral, reddish discoloration at head region of epididymides (Animal No 61), unilateral hydronephrosis (Animal No 212). These lesions could be considered as spontaneous or incidental in nature with no treatment related significance (APPENDIX 13).

*TABLE F: Gross Findings – Summary by Groups*

| *Group N°* | | *G1* | | *G2* | | *G3* | | *G4* | | *G5* | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Dose (mg/kg b. wt./day)* | | *0* | | *0* | | *2* | | *5* | | *10* | |
| *Organs & Lesions* | *Sex* | *M* | *F* | *M* | *F* | *M* | *F* | *M* | *F* | *M* | *F* |
| | *N° of Animals* | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* |
| ***EXTERNAL EXAMINATION*** | | | | | | | | | | | |
| *No abnormality detected* | | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* | *10* |
| ***INTERNAL EXAMINATION*** | | | | | | | | | | | |
| ***Epididymides*** | | | | | | | | | | | |
| *(unilateral, left) Reddish discoloration* | | *0* | *X* | *0* | *X* | *0* | *X* | *1* | *X* | *0* | *X* |

The above finding was noted in only 1/10 male rats at a MD; it was not observed at a HD and was not associated with any histopathology finding; it may be considered spontaneous.

**Organ weights***: No changes in organ weight were observed in Pitavastatin Magnesium (including on liver and kidney weights) and LIVALO® (Pitavastatin) treated animals compared with placebo/control groups. Overall organ weight between animals treated with Pitavastatin Tablets 4 mg (Magnesium salt) and LIVALO® (Pitavastatin) Tablets 4 mg was comparable (APPENDIX 13).*

**Histopathology:**

In the original NDA application, histopathology summary Tables were not provided. These were requested from the sponsor at the time of filing, which were then provided by the sponsor on 7/2015. Histopathological observation revealed lesion (hyperplasia/hyperkeratosis) in non-glandular stomach with pitavastatin magnesium, and with LIVALO.

*The incidence of the lesion in all rats of Pitavastatin Magnesium high dose- G5) was almost identical to LIVALO (high dose group-G8), while in female the incidence of lesion was lower (3/10) with Pitavastatin Magnesium (mid dose group G4) as compared to LIVALO (G7 group it was in 8/10 animals). Severity of lesions in animals treated with Pitavastatin Magnesium was marginally less as compared to LIVALO.*

*After 14 days of treatment free period, one female in LIVALO group showed the lesion while none of the animals in Pitavastatin magnesium group showed it (APPENDIX 13).*

*Table.* Histopathology showed lesions (hyperplasia/hyperkeratosis) in non-glandular stomach with pitavastatin magnesium, and with LIVALO.

| Lesion | Males | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 | G10 | G11 |
| Hyperplasia/ hyperkeratosis | 0 | 0 | 0 | 8 | 10 | 2 | 9 | 10 | 0 | 0 | 0 |

| Lesion | Females | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 | G10 | G11 |
| Hyperplasia/ hyperkeratosis | 0 | 0 | 0 | 3 | 9 | 0 | 8 | 10 | 0 | 0 | 1 |

Additionally in males at a HD of 10 mg/kg/day, toxicity was noted in the adrenal gland with Pitavastatin magnesium (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex of minimal severity in 1/10 vs 0/10 with Livalo). In females, no significant histopathology findings were noted in other organs.

Table. Males- Histopathology findings in the main study rats with Pitavastatin magnesium.

**Summary of Histopathological Examination**

| Group N° | | Number of animals showing lesions in group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
| Dose (mg/kg b. wt./day) | | 0 | 0 | 2 | 5 | 10 | 2 | 5 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M |
| **Eyes** | | | | | | | | | |
| **Rosettes, retinal,** | | | | | | | | | |
| focal,(+) | | 1 | 1 | X | X | 0 | X | X | 0 |
| **Harderian glands** | | | | | | | | | |
| **Pigmentation, luminal,** | | | | | | | | | |
| multifocal,(2+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| **Pituitary gland** | | | | | | | | | |
| **Cyst, pars distalis,** | | | | | | | | | |
| focal,(+) | | 0 | 2 | X | X | 0 | X | X | 0 |
| **Thymus** | | | | | | | | | |
| **Hemorrhages, medulla,** | | | | | | | | | |
| multifocal,(+) | | 0 | 1 | X | X | 1 | X | X | 1 |
| **Hyperplasia, epithelial cells,** | | | | | | | | | |
| focal,(+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| **Lungs including main bronchi** | | | | | | | | | |
| **Hemorrhages, alveolar,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | X | X | 0 | X | X | 1 |
| focal,(1+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| multifocal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| multifocal,(1+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| **Spleen** | | | | | | | | | |
| **EMH, erythroid, red pulp,** | | | | | | | | | |
| multifocal,(+) | | 0 | 0 | X | X | 1 | X | X | 0 |
| diffuse,(+) | | 0 | 2 | X | X | 0 | X | X | 0 |
| **Adrenal Gland** | | | | | | | | | |
| **Vacuolation, zona fasciculata,** | | | | | | | | | |
| diffuse,(+) | | 1 | 1 | X | X | 4 | X | X | 2 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

Table. Males- Histopathology findings in the main study rats with Pitavastatin magnesium continued.

**Summary of Histopathological Examination (Continued)**

| Group N° | | Number of animals showing lesions in group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
| Dose (mg/kg b. wt./day) | | 0 | 0 | 2 | 5 | 10 | 2 | 5 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M |
| **Kidneys** | | | | | | | | | |
| **Basophilic/Regenerating tubules, cortex,** | | | | | | | | | |
| focal,(+) | | 1 | 0 | X | X | 1 | X | X | X |
| multifocal,(+) | | 0 | 0 | X | X | 1 | X | X | X |
| **Dilatation, tubular, cortex,** | | | | | | | | | |
| multifocal,(+) | | 0 | 0 | X | X | 1 | X | X | X |
| **Epididymides** | | | | | | | | | |
| **Infiltration, MNC, interstitial, corpus,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | X | 0 | 0 | X | X | 1 |
| **(Bilateral) Necrosis, tubular,** | | | | | | | | | |
| focal,(3+) | | 0 | 0 | X | 1 | 0 | X | X | 0 |
| **Stomach** | | | | | | | | | |
| **Non glandular: Hyperplasia/Hyperkeratosis, mucosal,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | 0 | 3 | 1 | 0 | 1 | 0 |
| focal,(1+) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| multifocal,(+) | | 0 | 0 | 0 | 3 | 2 | 2 | 4 | 0 |
| multifocal,(1+) | | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| diffuse,(+) | | 0 | 0 | 0 | 1 | 3 | 0 | 3 | 2 |
| diffuse,(1+) | | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 4 |
| diffuse,(2+) | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 2 |
| diffuse,(3+) | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Non glandular: Parakeratosis, mucosal,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| **Non glandular: Infiltration, PMNC, submucosal,** | | | | | | | | | |
| focal,(1+) | | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Glandular: Infiltration, PMNC, submucosal,** | | | | | | | | | |
| multifocal,(+) | | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

Table. Males- Histopathology findings in the main study-male rats with Pitavastatin magnesium continued.

**Summary of Histopathological Examination (Continued)**

| Group N° | | Number of animals showing lesions in group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
| Dose (mg/kg b. wt./day) | | 0 | 0 | 2 | 5 | 10 | 2 | 5 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M | 10 M |
| **Liver** | | | | | | | | | |
| **Altered foci, clear cell,** | | | | | | | | | |
| focal,(+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| **Prostate gland** | | | | | | | | | |
| **Infiltration, MNC, interstitial,** | | | | | | | | | |
| focal,(+) | | 0 | 2 | X | X | 0 | X | X | 0 |
| multifocal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| multifocal,(1+) | | 0 | 0 | X | X | 0 | X | X | 1 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

Table. Females-Histopathology in the main study rats:

**Summary of Histopathological Examination (Continued)**

| Group N° | | Number of animals showing lesions in group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
| Dose (mg/kg b. wt./day) | | 0 | 0 | 2 | 5 | 10 | 2 | 5 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F |
| **Eyes** | | | | | | | | | |
| **Rosettes, retinal,** | | | | | | | | | |
| focal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| **Harderian glands** | | | | | | | | | |
| **Pigmentation, luminal,** | | | | | | | | | |
| diffuse,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| **Thymus** | | | | | | | | | |
| **Hemorrhages, medulla,** | | | | | | | | | |
| multifocal,(+) | | 1 | 0 | X | X | 0 | X | X | 2 |
| multifocal,(1+) | | 0 | 0 | X | X | 0 | X | X | 2 |
| **Lungs including main bronchi** | | | | | | | | | |
| **Hemorrhages, alveolar,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | X | X | 1 | X | X | 0 |
| focal,(2+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| multifocal,(1+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| diffuse,(3+) | | 0 | 1 | X | X | 0 | X | X | 0 |
| **Spleen** | | | | | | | | | |
| **EMH, erythroid, red pulp,** | | | | | | | | | |
| multifocal,(+) | | 0 | 1 | X | X | 1 | X | X | 1 |
| diffuse,(+) | | 1 | 0 | X | X | 1 | X | X | 0 |
| **Pancreas** | | | | | | | | | |
| **Atrophy, lobular,** | | | | | | | | | |
| focal,(+) | | 1 | 1 | X | X | 0 | X | X | 0 |
| **Kidneys** | | | | | | | | | |
| **Basophilic/Regenerating tubules, cortex,** | | | | | | | | | |
| focal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

**Summary of Histopathological Examination (Continued)**

| Group N° | | Number of animals showing lesions in group | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 |
| Dose (mg/kg b. wt./day) | | 0 | 0 | 2 | 5 | 10 | 2 | 5 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F | 10 F |
| **Kidneys** | | | | | | | | | |
| **Infiltration, MNC, interstitial,** | | | | | | | | | |
| focal,(1+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| **Stomach** | | | | | | | | | |
| **Non glandular: Hyperplasia/Hyperkeratosis, mucosal,** | | | | | | | | | |
| multifocal,(+) | | 0 | 0 | 0 | 1 | 3 | 0 | 3 | 0 |
| multifocal,(1+) | | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| diffuse,(+) | | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 2 |
| diffuse,(1+) | | 0 | 0 | 0 | 1 | 3 | 0 | 2 | 2 |
| diffuse,(2+) | | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 4 |
| diffuse,(3+) | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| **Non glandular:Parakeratosis, mucosal,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| **Non glandular: Infiltration, PMNC, submucosal,** | | | | | | | | | |
| multifocal,(+) | | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 |
| **Glandular: Dilatation, glandular,** | | | | | | | | | |
| focal,(+) | | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 |
| **Liver** | | | | | | | | | |
| **Infiltration, MNC, periportal,** | | | | | | | | | |
| focal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |
| **Altered foci, clear cell,** | | | | | | | | | |
| multifocal,(+) | | 1 | 0 | X | X | 0 | X | X | 0 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

Histopathology findings in the recovery animals (males and females):

**Summary of Histopathological Examination (Continued)**

| Group N° | | Number of animals showing lesions in group | | |
|---|---|---|---|---|
| | | G9 | G10 | G11 |
| Dose (mg/kg b. wt./day) | | 0 | 10 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 M | 10 M | 10 M |
| Stomach | | | | |
| Glandular: Infiltration, PMNC, submucosal, | | | | |
| focal,(1+) | | 1 | 0 | 0 |

| Group N° | | Number of animals showing lesions in group | | |
|---|---|---|---|---|
| | | G9 | G10 | G11 |
| Dose (mg/kg b. wt./day) | | 0 | 10 | 10 |
| Organs & Lesions | N° of Animals and sex | 10 F | 10 F | 10 F |
| Kidneys | | | | |
| Atrophic tubules (Hydronephrosis) | | | | |
| - present | | X | X | 1 |
| Stomach | | | | |
| Non glandular: Hyperplasia/Hyperkeratosis, mucosal, | | | | |
| multifocal,(+) | | 0 | 0 | 1 |

**Note:**

I. Organs not included in table did not reveal any gross and histopathological findings.

II. 'X' = Organs not examined as per study plan/sex difference.

III. Severity grade: minimal (+), mild (1+), moderate (2+), severe (3+) and very severe (4+)

Sponsor's conclusions on histopathology are provided below:

**Discussion:** Histopathological observation revealed lesion (hyperplasia/hyperkeratosis) in non glandular stomach of test item treated animals as well as reference item treated animals. The incidence of the lesion in test item treated groups (high dose – G5 and mid dose – G4) was almost identical to incidence of counter groups of reference item (G8 and G7 respectively).

None of the low dose (G3) animal from test item treated group showed the lesion, while 2 males from reference item low dose group (G6) were affected by it.

After 14 days of treatment free period, one female of reference item group showed the lesion while none of the animals from test item group showed it.

(b) (4)

[redacted]

Reviewer's summary: At a HD of 10 mg/kg/day, the target organs of toxicity with the current drug product Pitavastatin magnesium and Livalo were similar, i.e. lesions in the non-glandular stomach (combined males + females 0/40, 0/20, 11/20, 19/20 vs 0/40, 2/20, 17/20, 20/20 with Livalo at 0, 2, 5, 10 mg/kg/day respectively). Other findings noted in males at a HD with Pitavastatin magnesium were in the adrenals (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex with minimal severity in 1/10 vs 0/10 with Livalo). In females, no significant toxicity was noted in the other organs. The stomach findings were not present at the end of the drug free recovery period, with Pitavastatin magnesium, suggesting these were reversible.

**Toxicokinetics**:

The exposures of Pitavastatin magnesium in males and females were slightly higher on day 28 at low and mid doses (males 859, 3522, 7521 ng.h/ml at 1, 5, and 10 mg/kg/day, respectively; in females were 630, 2956, 6893 ng.h/ml respectively) than on day 1 (males 730, 2451, 7260 ng.h/ml respectively; females 587, 2650, 9883 ng.hr/ml respectively).

Similarly the exposures of Livalo in males and females were slightly higher on day 28 at low and mid doses (males 647, 3823, 6172 ng.h/ml respectively; females 837, 3389, 10849 ng.h/ml respectively) than on day 1 (males 610, 2203, 7683 ng.h/ml at 1, 5, and 10 mg/kg/day respectively; in females were 608, 2395, 8908 ng.h/ml, respectively)

Table. Exposures of Pitavastatin magnesium and Livalo in a 28-day toxicity study in rats

| | Pitavastatin magnesium AUC exposures (males/females) in ng.h/ml | | |
|---|---|---|---|
| Doses (mg/kg/day) | 2 | 5 | 10 |
| Day 1 | 730/587 | 2451/2650 | 7260/9883 |
| Day 28 | 859/630 | 3522/2956 | 7521/6893 |
| | | | |
| | Livalo AUC exposures (males/females) in ng.h/ml | | |
| Day 1 | 610/608 | 2203/2395 | 7683/8908 |
| Day 28 | 647/837 | 3823/3389 | 6172/10849 |

Sponsor's description of TK is provided below:

*The peak plasma concentration (Tmax) was rapidly attained at 0.5 to 1 h with the current drug product vs LIVALO on days 1 and 28 at the all doses. There was marginal evidence of accumulation on repeat dosing with Zydus Pitavastatin and Livalo. The accumulation index (AUC Day 28/Day 1) ranged from 0.7 to 1.4, with the exception of LIVALO at a MD in males. The mean elimination half-life of Zydus's pitavastatin and LIVALO ranged from 1.9 h to 5.9 h and 1.1 h to 7.0 h across the doses in both the sexes on days 1 and 28, respectively.*

*No consistent gender effect in TK were evident on day 1. At the LD of 2 mg/kg/day of Zydus's Pitavastatin, exposure was similar in males and females (Cmax: 299 and 264 ng/mL, respectively; AUClast: 729 and 587 ng.h/mL, respectively); similarly with 2 mg/kg/day of LIVALO, exposures were similar in males and females (Cmax: 183 and 163.86 ng/mL, respectively; AUC: 610 and 608 ng.h/mL). At the HD of 10 mg/kg/day Pitavastatin magnesium, the Cmax was lower in males than females (2008 and 6492 ng/mL, respectively), while the overall exposure was similar in both sexes (AUClast: 7259 and 9883 ng.h/mL, respectively). With 10 mg/kg b. wt./day LIVALO also, the exposure was marginally lower in males than females (Cmax: 2013 and 5474 ng/mL, respectively; AUClast: 7683 and 8908 ng.h/mL, respectively).* See the Table below.

Table. TK of Pitavastatin magnesium and the reference drug Livalo in a 4-week study in rats.

| Drug | Sex | Day | Dose (mg/kg) | Dose fold Increase[a] | $T_{max}$ (h) | $C_{max}$ (ng/mL)[b] | $C_{max}$ fold increase[a] | $AUC_{last}$ (ng.h/mL) | $AUC_{last}$ fold increase[a] | AI[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| Pitavastatin Tablets 4 mg (Magnesium salt) | Male | 1 | 2 | - | 0.5 | 299.22 ± 142.36 | - | 729.90 | - | - |
| | | | 5 | 2.5 | 1.0 | 857.25 ± 108.04 | 2.9 | 2450.58 | 3.4 | - |
| | | | 10 | 5 | 1.0 | 2008.80 ± 40.54 | 6.7 | 7259.78 | 9.9 | - |
| | | 28 | 2 | - | 1.0 | 249.32 ± 92.47 | - | 858.89 | - | 1.2 |
| | | | 5 | 2.5 | 0.5 | 2019.81 ± 1036.87 | 8.1 | 3521.88 | 4.1 | 1.4 |
| | | | 10 | 5 | 0.5 | 3566.22 ±2106.65 | 14.3 | 7521.06 | 8.8 | 1.0 |
| | Female | 1 | 2 | - | 0.5 | 264.46 ± 66.97 | - | 587.36 | - | - |
| | | | 5 | 2.5 | 0.5 | 930.18 ± 257.02 | 3.5 | 2649.88 | 4.5 | - |
| | | | 10 | 5 | 0.5 | 6492.66 ± 384.73 | 24.6 | 9883.03 | 16.8 | - |
| | | 28 | 2 | - | 0.5 | 231.26 ± 42.76 | - | 630.42 | - | 1.1 |
| | | | 5 | 2.5 | 0.5 | 2184.39 ± 1004.68 | 9.4 | 2955.80 | 4.7 | 1.1 |
| | | | 10 | 5 | 0.5 | 4393.44 ± 1044.54 | 19.0 | 6893.40 | 10.9 | 0.7 |
| LIVALO® (Pitavastatin) tablets | Male | 1 | 2 | - | 1.0 | 183.92 ± 78.63 | - | 610.21 | - | - |
| | | | 5 | 2.5 | 0.5 | 964.41 ± 505.26 | 5.2 | 2202.91 | 3.6 | - |
| | | | 10 | 5 | 0.5 | 2013.84 ± 1089.58 | 10.9 | 7683.07 | 12.6 | - |
| | | 28 | 2 | - | 1.0 | 200.22 ± 45.71 | - | 646.91 | - | 1.1 |
| | | | 5 | 2.5 | 1.0 | 1078.19 ± 175.57 | 5.4 | 3832.15 | 5.9 | 1.7 |
| | | | 10 | 5 | 0.5 | 2261.40 ± 323.05 | 11.3 | 6171.55 | 9.5 | 0.8 |
| | Female | 1 | 2 | - | 0.5 | 163.86 ± 47.93 | - | 608.62 | - | - |
| | | | 5 | 2.5 | 0.5 | 1172.12 ± 226.71 | 7.2 | 2395.22 | 3.9 | - |
| | | | 10 | 5 | 0.5 | 5474.21 ± 2765.61 | 33.4 | 8908.51 | 14.6 | - |
| | | 28 | 2 | - | 0.5 | 490.29 ± 167.58 | - | 836.84 | - | 1.4 |
| | | | 5 | 2.5 | 0.5 | 2102.18 ± 624.79 | 4.3 | 3388.60 | 4.0 | 1.4 |
| | | | 10 | 5 | 0.5 | 5280.21 ± 701.34 | 10.8 | 10849.35 | 13.0 | 1.2 |

Sponsor's conclusions on this 28-day study are stated below:

*It was concluded from the above findings that repeated oral administration of Pitavastatin Tablets 4 mg (Magnesium salt) up to 10 mg/kg b. wt /day over a period of four weeks to Wistar rats was well tolerated in this study. Treatment related effects such as hyperplasia and hyperkeratosis noticed in non-glandular stomach was found to be reversible at 10 mg/kg b. wt./day with test item; Pitavastatin Tablets 4 mg (Magnesium salt) similar to reference item, LIVALO® (Pitavastatin) Tablets 4 mg treated groups.*
*The no-observed-adverse-effect level (NOAEL) of Pitavastatin Tablets 4 mg (Magnesium salt) supplied by Cadila Healthcare Limited, Gujarat is considered to be 2 mg/kg b. wt./day under these study conditions in Wistar rats*

**Reviewer's summary**: In a 28-day oral toxicity study in rats with a 2-week drug-free recovery period, doses of 0 (vehicle), 0 (placebo), 2, 5, 10 mg/kg/day of Pitavastatin magnesium tablets were administered to five groups of rats (n= 10 /sex /dose). Three additional group of rats were similarly administered the listed drug, Livalo tablets (2, 5, 10 mg/kg/day) for comparison. The exposures of Pitavastatin magnesium in males/females were slightly higher on day 28 at LD and MD (males 859/630, 3522/2956, 7521/6893 ng.h/ml at 2, 5, and 10 mg/kg/day respectively) vs day 1 (males 730/587, 2451/2650, 7260/9883 ng.h/ml respectively).

Similarly, the exposures of Livalo in males and females were slightly higher at low and mid doses on day 28 (males 647/837, 3823/3389, 6172/10849 ng.h/ml respectively) vs day 1 (males 610/608, 2203/2395, 7683/8908 ng.h/ml at 1, 5, and 10 mg/kg/day respectively). Thus the TK in general were similar with both drugs.

No significant clinical signs were noted with both drugs (current or listed drug). In males at a HD of Zydus's Pitavastatin magnesium decreased body weight gains were noted in the recovery group vs the controls (13.7* vs 16.6 g with controls, *p<0.05), but not with the RD (Livalo). No effects on body weights or weight gains in females were noted. No effects on food consumption, hematology or clinical chemistry parameters were noted. In neuro-behavioral assessments in males, decreased hind-limb foot splay was noted at a HD of Zydus Pitavastatin magnesium and at MD of Livalo vs controls (71.7*, 64.4* vs 89.3 mm in controls, *p<0.05). At the end of the drug free recovery period, the decreased hind-foot splay was still noted at a HD of Zydus's Pitavastatin magnesium, but not with Livalo (62.8** vs 76.5 mm, **p<0.01). *Sponsor states that these changes were not associated with any other muscular activity hence it could not be considered as toxicological relevance.* However, note that this change was observed at a HD of Pitavastatin magnesium; it was not reversible, but there was a substantial safety margin, as it occurred at 24-fold the human therapeutic dose of 4 mg/day.

Histopathology findings at a HD of 10 mg/kg/day with the Pitavastatin magnesium and Livalo were similar, i.e. both products produced lesions in the non-glandular stomach (hyperplasia/ hyperkeratosis in males + females 0/20, 0/20, 11/20, 19/20 vs 0/20, 2/20, 17/20, 19/20 with Livalo at 0, 2, 5, 10 mg/kg/day respectively). Additionally, at the HD in males with Pitavastatin magnesium findings were noted in the adrenals (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex in 1/10 vs 0/10 with Livalo). In females, no significant toxicity was noted in the other organs. Also note that drug- related effects such as hyperplasia and hyperkeratosis noticed in non-glandular stomach were reversible at 10 mg/kg/day of Pitavastatin magnesium.

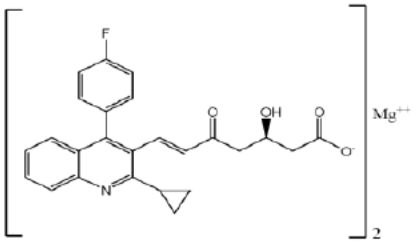
Note that only doses up to 10 mg/kg/day of the current and reference drug product were used; at this dose, except for the toxicity in the non-glandular stomach, no significant toxicity was noted in the other organs; higher doses of the Zydus's Pitavastatin magnesium drug product would have

more clearly established the target organs of toxicity. However since similar toxicity was noted with both the current product and listed drug product Livalo, the study is considered acceptable.

The NOAEL doses of the drug in a 4-week oral toxicity study in rats is considered 2 mg/kg/day as histopathology findings were noted in the stomach at a MD and HD of Pitavastatin magnesium. In general similar histopathology findings were noted with the listed drug Livalo. This NOAEL of 2 mg/kg/day (or 12 mg/m$^2$/day) provides the safety margin of 5 X in human subjects (4 mg/day or 0.067 mg/kg/day or 2.47 mg/m$^2$/day), based on body surface area.

**Impurities in the Zydus's Pitavastatin magnesium**

According to the FDA chemist, both Livalo and the new product contain the, (b) (4) (or (b) (4) impurity. The chemist on this drug substance, Dr. Erika Englund pointed out that (b) (4) contains (b) (4). This is the only impurity with a structural alert. The level of this degradant is higher ( (b) (4) ) in Pitavastatin magnesium compared to the level in the approved drug product Livalo (NDA 22363), where it is present at (b) (4) *based on the maximum recommended dose of Livalo of 4 mg/day).*




As noted in the certificate of analysis (on pages 25-26), (b) (4) (or (b) (4) ) was present at only (b) (4) % in Pitavastatin magnesium along with the total degradation products of (b) (4) %, and this batch was tested in the 28-day toxicity study (batch # EMN268), compared to the specification of (b) (4) of NMT (b) (4). Other impurities such as (b) (4) or (b) (4) were shown not to be present in the certificate of analysis (or COA). The impurity levels in the listed drug Livalo are not provided in the COA for Livalo (see page 26).

The specified impurity for (b) (4) in Zydus's Pitavastatin magnesium is NMT (b) (4) (see Table below) and the total daily intake of this degradation product is (b) (4) (the maximum dose of this drug product administered will be 4 mg/day).

Table. Specified degradation products in the drug product are shown below:

Specified Degradation Products (Shelf Life) – for drug product:

| Chemical Name | Code# | MDD | IT | QT | TDI of Degradation Product | Proposed AC for Unspecified Degradation Product | Proposed AC for Specified Degradation Product | Justification if AC > QT for Specified Degradation Product |
|---|---|---|---|---|---|---|---|---|
| (b) (4) | | | | | | | | |

NMT: Not More Than; MDD: Maximum Daily Dose; IT: Identification Threshold; QT: Qualification Threshold
TDI: Total Daily Intake; AC: Acceptance criteria

Table. Total degradants (impurities) in the drug product Pitavastatin magnesium are no more than (NMT) (b) (4) %

| Quality Attributes of the drug product | Target | CQA (Yes /No) | Justification |
|---|---|---|---|
| Friability | (b) (4) | No | (b) (4) |
| Hardness | | Yes | |
| Disintegration Time | | Yes | |
| Identification | | Yes* | |
| Assay | | Yes | |
| Degradation product | | Yes | |
| (b) (4) | | | |

The recommended doses of Zydus's Pitavastatin magnesium are up to 4 mg/day. Therefore 4 mg (or 4000 mcg) will have up to (b) (4) assuming the 60 kg average weight). In the 28-day toxicity study in rats, doses of up to 10 mg/kg/day (or 10,000 mcg/kg/day) of Pitavastatin magnesium were tested in rats, which had up to (b) (4) % impurities; of which (b) (4) was (b) (4) (b) (4)

Therefore based on above calculation, (b) (4) is qualified by the 28-day study, as the amounts of this degradant in the toxicity study in rats were much higher (b) (4) than the therapeutic doses that will be administered to humans (b) (4)

**2.6.6.4. Genetic toxicology**: No gene-toxicity studies have been conducted with this drug product (Pitavastatin magnesium). However, sponsor has stated the following information in the CMC section (module 2 /quality-overall summary / pages 29-33 of 107) which mentions the toxicity studies by quantitative structure activity relationship (QSAR) software, see below

**Genotoxicity Impurity (section 3.2.S.3.2)**:
*Drug substance manufacturer (i.e. Cadila Healthcare Limited, Dabhasa, India) has been checked for genotoxicity structural alert for the Impurities, Key starting materials (KSM) and intermediates present in the Pitavastatin Magnesium and the details are provided below*:

| Chemical name (Starting material / Raw materials) | Impurity Type | Information Source |
|---|---|---|
| (b) (4) | | (b) (4) |

| Chemical name (Starting material / Raw materials) | Impurity Type | Information Source |
|---|---|---|
| | (b) (4 | (b) (4) |


*Sponsor states "From the both table it can be concluded that there is no structural alert for genotoxicity identified in any of the impurities, key starting material and intermediates associated with the Pitavastatin Magnesium. Detailed **Toxicity Prediction Report** for this study has been provided herewith. Genotoxic evaluation reveals that there are no such impurities generated or chemicals used in the manufacturing process of Pitavastatin Magnesium that can pose any genotoxic concern. Thus, no further studies are required for this application to assess safety of genotoxic impurities".*

Thus, according to the sponsor, no structural alert were found for Ames TA100 by QSAR method (ToxtTree); hence it was concluded that these are non-genotoxic.

As stated before, there is a (b) (4) degradant, which is an impurity with a potential structural alert, although this degradant is controlled in the drug product, the level of this impurity allowed by the NMT (b) (4)% specification in the current drug product is higher (b) (4) compared to the level in the approved drug product Livalo (which has this present at (b) (4) ), see the Table below, which shows the comparison of impurities in the current drug product Pitavastatin magnesium and Livalo.

The following Table shows the comparison of impurities in the current drug product Pitavastatin magnesium and Livalo, it is provided by the applicant in the CMC section. The FDA chemist flagged the compound [redacted] (b) (4) as a potential structural alert.

**Comparison of impurities identified in Livalo tablets and Zydus Pitavastatin Magnesium tablets:**

Regarding qualification of impurities, we would like to inform the agency that maximum daily dose of Pitavastatin magnesium is 4 mg/day. As per ICH-Q3B(R2) guidance, threshold for maximum daily dose of 4 mg is tabulated below:

| | |
|---|---|
| **Reporting Thresholds** | 0.10 % |
| **Identification Thresholds** | 0.5 % |
| **Qualification Thresholds** | 1.0 % |

To demonstrate safety of salt change for Pitavastatin Magnesium Tablet when compared with RLD Livalo i.e. Pitavastatin Calcium Tablet, we have done following comparisons.

Livalo tablets close to expiry were subjected to analysis for impurity determination and compared with Pitavastatin Magnesium Tablets using validated analytical methodology involving PDA detector. All the impurities were qualified as per ICH-Q3B (R2) guidance.

**Table: Impurity profiles of Livalo tablet and Pitavastatin Magnesium Tablet, finished product (Qualified as per ICH-Q3B (R2))**

| Impurity | Origin of impurity | Livalo 4 mg tablet 3095506 Exp dt. Oct'14 | Pitavastatin Magnesium Tablet as manufactured by Zydus Cadila on March 2013 | | |
|---|---|---|---|---|---|
| | | | EMN 268 | EMN 269 | EMN 270 |
| [redacted] (b) (4) | | | | | |

We requested the consult from the FDA Computational Science Center (CSC) to assess the definitive determination of QSAR for the (b) (4) impurity present in the drug product Pitavastatin magnesium. See the results of the consult below:

*The (b) (4) a pitavastatin degradant, has been evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: Derek Nexus 4.1.0 (DX), Leadscope Model Applier 2.0.3-1 (LMA), and CASE Ultra 1.6.0.0 (CU). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify a positive overall call. All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.*
*The (Q)SAR assessment of mutagenic potential is consistent with recommendations described in the final ICH M7 guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). Based on the entire weight of evidence, (b) (4) is predicted to be negative for bacterial mutagenicity.*

**Bacterial Mutagenicity (Q)SAR Predictions**[1]

(b) (4)

| Software | *Salmonella* Mutagenicity | *E. coli/TA102* Mutagenicity |
|---|---|---|
| *Derek Nexus* | - | - |
| *Leadscope Model Applier* | - | - |
| *CASE Ultra* | - | NC |
| Overall Software Prediction | - | - |
| **Overall Expert Prediction** | - | - |

(b) (4) is predicted to be negative for *Salmonella* and *E.coli/TA102* mutagenicity.

Also note that the Livalo label (provided by the current applicant) states that it was negative in most gene toxicity, see below:

"Pitavastatin is not genotoxic, by weight of evidence. Pitavastatin was positive in a chromosomal aberration assay with metabolic activation in Chinese hamster lung (CHL) cells. The positive result was obtained at a concentration of pitavastatin that was close to that which caused 50% cytotoxicity with metabolic activation. Pitavastatin was negative for genotoxicity in a chromosomal aberration assay without metabolic activation in CHL cells. Pitavastatin was also negative in an Ames reverse mutation battery, *in vivo* mouse and rat micronucleus assays, an *in vivo/in vitro* single cell gel (Comet assay), and an *in vivo/in vitro* rat unscheduled DNA synthesis (UDS) assay. *(Ref: Drug Approval Package (FDA) Pharmacology Review(S) page no. 129)".*

In conclusion, no additional gene-toxicity studies are required for Zydus's Pitavastatin magnesium.

**OVERALL CONCLUSIONS AND RECOMMENDATIONS**

Pitavastatin is an HMG-CoA reductase inhibitor (statin); it is a synthetic lipid-lowering agent for oral administration. Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved in the biosynthesis of cholesterol. Pitavastatin calcium is currently marketed by Kowa Co., LTD, under NDA 022363 (Livalo). Zydus Pharmaceuticals is developing pitavastatin magnesium tablets at the same dosage strengths (1 mg, 2 mg, and 4 mg) as the currently marketed drug Livalo, for a proposed 505(b)(2) marketing application.

Note that Kowa's approved drug product is Pitavastatin calcium (or Livalo), while Zydus drug product is Pitavastatin magnesium. In the current 505(b)(2) application, Zydus has conducted one 28 day bridging toxicity study in rats, which is reviewed here-in.

In a 28-day oral toxicity study of Pitavastatin magnesium tablets in rats, with a 2-week drug recovery period, doses of 0 (vehicle0, 0 (crushed placebo tablets), 2, 5, 10 mg/kg/day were administered to five groups of rats (n=10/sex/dose). The listed drug (LD) Livalo tablets was similarly administered to 3 additional group of rats (at 2, 5, 10 mg/kg/day) for comparison. The plasma exposures (AUC) with Pitavastatin magnesium in males/females were generally comparable to that for Livalo; on day 28 in males and females administered Pitavastatin magnesium were 859/630, 3522/2956, 7521/6893 ng.h/ml at 1, 5, and 10 mg/kg/day, respectively (vs with Livalo were 647/837, 3823/3389, 6172/10849 ng.h/ml respectively). Thus the TK in general appear to be similar with both drugs, with the exception of the HD Livalo in females.

No significant clinical signs were noted with the either drug (current or LD). In males at a HD of Zydus's Pitavastatin, body weight gains were lower in the recovery group vs the controls (13.7* vs 16.6 g with controls, *p<0.05) but not with the RD (Livalo); no effects on body weights or weight gains in females were noted. Note that the above body weight changes are not considered biologically significant. *No effects on food consumption, hematology or clinical chemistry parameters were noted.* In neuro-behavior assessments in males, decreased *hind-limb foot splay was noted* at a HD of Zydus's Pitavastatin and at MD of Livalo vs controls (71.7*, 64.4* vs 89.3 mm with controls, *p<0.05). At the end of the drug free recovery period, the decreased hind-limb foot splay was noted with a HD of Zydus's Pitavastatin, but not with Livalo (62.8** vs 76.5 mm, **p<0.01). *According to the sponsor these changes were not associated with any other muscular activity hence these were not considered toxicological relevant*. Note that these neuro-behavior findings were observed not only during treatment at a HD with Pitavastatin magnesium, but also after the drug-free recovery period, suggesting that these are not reversible. However, but occurred at 24-fold the human therapeutic dose of 4 mg/day, suggesting there is significant safety margin at the maximum recommended human dose.

The HD of 10 mg/kg/day produced similar histopathology findings in the non-glandular stomach with both drugs in male and female rats (hyperplasia and hyperkeratosis in 0/40, 0/20, 11/20, 19/20 vs 0/40, 2/20, 17/20, 20/20 with Livalo at 0, 2, 5, 10 mg/kg/day respectively). Other findings noted in males at a HD with Pitavastatin magnesium were in the adrenals (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex in 1/10 vs 0/10 with Livalo). In females, no significant toxicity was noted in the other organs. The histopathology findings in the non-glandular stomach were all reversible with Pitavastatin magnesium.

Thus the subtle toxicity was noted with the current drug product, which was not noted with the LD. At the HD, findings included lower body weight gains in males at the end of recovery periods

(13.7* vs 16.6 g with controls, *p<0.05), and decreases in hind-limb foot splay at a HD, but not with Livalo (62.8** vs 76.5 mm, **p<0.05). Additionally, histopathology findings were noted in males at a HD with Pitavastatin magnesium in the adrenals (diffuse vacuolation in the zona fasciculata of a minimal severity in 4/10 vs 2/10 with Livalo) and in the kidney (multifocal findings in the dilatation of tubular cortex in 1/10 vs 0/10 with Livalo). These subtle differences in toxicity profile may represent natural biological variability in response to the Active pharmaceutical ingredients.

The NOAEL doses of the drug in a 4-week oral toxicity study in rats is considered to be 2 mg/kg/day as histopathology findings were noted in the stomach at a MD and HD of Pitavastatin magnesium. Note that in general similar histopathology findings were observed with the listed drug Livalo. This NOAEL of 2 mg/kg/day (or 12 mg/m$^2$/day) provides the safety margin of 5X in human subjects (4 mg/day or 0.067 mg/kg/day or 2.47 mg/m$^2$/day), based on the body surface area.

**Gene-toxicity**: The current drug (Zydus Pitavastatin magnesium) was not tested in any gene-toxicity studies, except the DMF holder states that that no structural alert for genotoxicity was identified in any of the impurities, or in the key starting material and intermediates associated with the Pitavastatin Magnesium (by QSAR analysis using ToxTree). The FDA chemist pointed out one impurity, i.e. (b) (4) (or (b) (4)), which could pose a structural alert. This degradant is present at up to (b) (4) (or at (b) (4) level) in a maximum recommended dose of 4 mg/day of Pitavastatin magnesium (b) (4) and although this degradant is also present in the reference drug Livalo at up to (b) (4)%, it was present at higher levels in the current Pitavastatin magnesium (up to (b) (4) in Livalo). This impurity was tested by the current applicant using QSAR analysis (using ToxTree), which was not considered adequate. Note that generally anything exceeding ICHQ3 (or with a structural alert for genotoxicity that's above 1.5 mcg/day) was considered for qualification. However, it was *evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using QSAR models and was predicted to be negative for bacterial mutagenicity.*

Thus all impurities including (b) (4) present in the Zydus's drug product (Pitavastatin magnesium) are considered qualified in the gene-toxicity studies.

**Safety evaluation**:

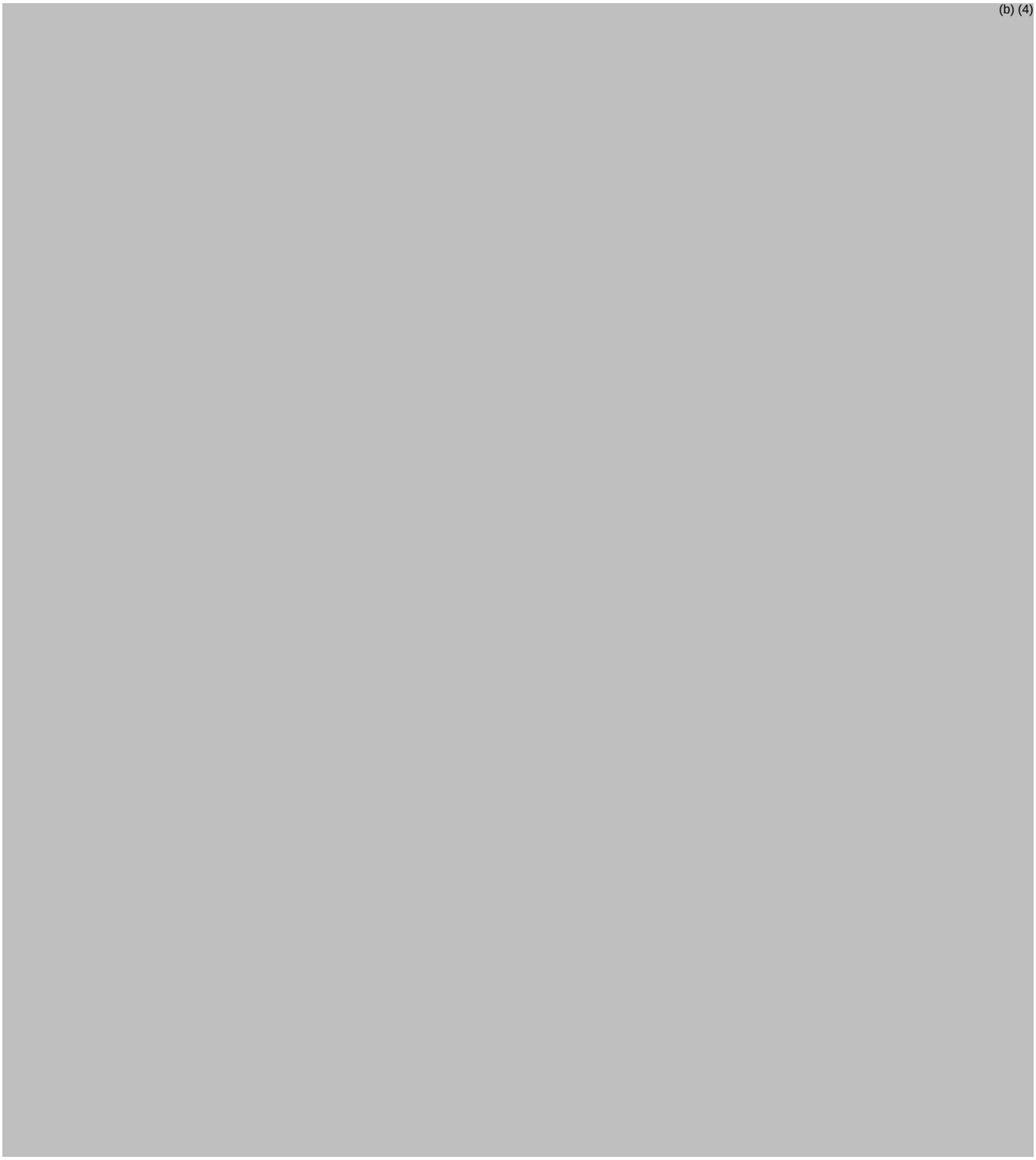
Zydus Pharmaceuticals has performed a 28-day bridging toxicity study in rats, comparing its Pitavastatin product to the reference drug Livalo. This 28-day toxicity study demonstrated that the two products are sufficiently comparable. No new concerning toxicities in the Zydus's Pitavastatin magnesium were identified. From the preclinical standpoint, approval of this application is recommended.

**Labeling Review**: The pharmacology toxicology label on Pitavastatin magnesium is similar to the approved drug product Livalo label from Kava pharmaceutical Ltd. In the current NDA application, the submitted label is reviewed, the applicant has replaced the word "Livalo" with their own proprietary name "ZYPITAMAG". The rest of the label is identical to the innovator's label.

From the pharmacology / toxicology point of view, the label is acceptable. The applicant's Pharmacology/ toxicology part of the label is stated below.

Following is sponsor's proposed label (from 7/16/2015 submission):

(b) (4)




### 8.4 Pediatric Use

Safety and effectiveness of ZYPITAMAG in pediatric patients have not been established.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 92 week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors.

In a 92 week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

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

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

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

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

### 13.2 Animal Toxicology and/or Pharmacology

***Central Nervous System Toxicity***

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

**Recommendation:** From the pharmacology/Toxicology point of view, approval of this application is recommended.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____

Concurrence Yes ___ No ___

cc: IND Arch

HFD-510

HFD-510/Elmore/antonipillai/whitehead.R/tran/roberts.M.

File name: nda 208379 (Pitavastatin magnesium)

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/s/

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INDRA ANTONIPILLAI
11/24/2015
From the Pharmacology/Toxicology point of view, approval of this application is recommended.

CALVIN L ELMORE
11/24/2015
I concur.

Signed off in DARRTS on 5/11/2015

45 Day Meeting Checklist

NONCLINICAL PHARMACOLOGY/TOXICOLOGY

**NDA Number**: NDA 208-379, it is a 505(b)(2) application. Reference drug is NDA 022-363 (Livalo, Pitavastatin calcium salt by Kowa Co.,Ltd. USA).

**Submission date**: 3/31/12015

**Sponsor**: Pitavastatin magnesium drug product is being developed by Cadila Healthcare Limited, Gujarat, India. Zydus Pharmaceutecals Inc, Penniington, NJ is a wholly owned subsidiary of the parent company, Cadila Healthcare Limited, India.

**Drug**: Pitavastatin magnesium salt, tablet strengths 1, 2, 4 mg. It is a 505(b)(2) application. The reference drug product is Pitavastatin calcium or Livalo, approved on 8/3/2009 (under NDA 022-363, by Kova Company Ltd. USA). Pitavastatin Magnesium is manufactured at Cadila Healthcare Limited, Gujarat, India (Type II DMF # (b) (4)

**Introduction**: Pitavastatin is a HMG-CoA reductase inhibitor (statin); Pitavastatin calcium is currently marketed by Kowa Co., LTD, USA. (NDA 022363 / Livalo). Cadila Healthcare Ltd., India has developed Pitavastatin magnesium Salt and they would like to market it, at the same dosage strengths as the listed drug (Pitavastatin calcium), for a proposed 505(b)(2) application.

**Indication**: It is a lipid-lowering agent, indicated for treatment of patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), Apo B and triglycerides (TG), over the dose range of 1 to 4 mg daily.

**Drug product**: Each film-coated tablet of pitavastatin contains 1.026 mg, 2.053 mg, or 4.106 mg of pitavastatin magnesium, which is equivalent to 1 mg, 2 mg, or 4 mg, respectively of free base.

**Brief history**: Initially on 6/25/2013, Zydus Pharmaceuticals USA Inc. (Zydus) submitted a new IND 117,674 for pitavastatin magnesium tablets (1 mg, 2 mg, and 4 mg pitavastatin magnesium). The sponsor outlined that they will perform two bridging clinical bioequivalence studies and a bridging nonclinical toxicology study to support their 505(b)(2) NDA application. The listed drug for Zydus' pitavastatin magnesium NDA was Livalo (pitavastatin calcium by Kowa Co. Ltd. under NDA 022363). Note that no nonclinical studies with Zydus' pitavastatin magnesium drug substance have been conducted under the above IND. However, Zydus previously proposed that the source of pitavastatin calcium comparator would not be Livalo, but a drug substance to be generated at the same facility as Zydus' pitavastatin magnesium, (i.e. Cadila Healthcare Limited, India).

We communicated to the sponsor on 7/30/13, 11/22/13 and again on 11/22/14 that they would need to use the Livalo as the comparator in their bridging toxicology study. We reiterated the need for the comparison as stated below.

"We acknowledge that "you provided a minimal analysis of the impurity profiles of your magnesium salt version of pitavastatin as it compares to that of Livalo. Reliance on physicochemical analysis to establish a bridge to the listed drug, Livalo, would require verification that all impurities needing qualification per ICH-Q3B(R2) and the CDER Guidance for Industry-". It is the sponsor's responsibility to identify and, if necessary, qualify potentially geno-toxic impurities, per guidance ICHM7".

In the current NDA 208-379, the sponsor has conducted one 28 day toxicity study in rats with their product and the reference drug Livalo, followed by a 14-day drug free recovery period. However, no gene-toxicity studies have been conducted to qualify the impurities/excipients/degradants in their drug product. The sponsor only stated that QSAR analyses have been completed but did not provide detailed information in the nonclinical section of the NDA.

The sponsor only stated that QSAR analyses have been completed but did not provide detailed information in the nonclinical section of the NDA.

| TEM: NDA 208-379 | YES | NO | COMMENT |
|---|---|---|---|
| 1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed? | Yes | | The current drug product is Pitavastatin magnesium salt and it refers to the previously approved drug product Pitavastatin calcium (by Kova Company, Ltd. USA, NDA 022-363 / Livalo. |
| 2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review? | Yes | | |

| | | | |
|---|---|---|---|
| 3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?<br><br>. | Yes | | A new 28-day bridging toxicology study n rats has been provided in the current NDA application. However, the summary Tables of the histopathology data are not well presented. The gross and histopathology data are combined n one Table and do not include all the details, and severity scores are not provided. Peer review of histopathology slides was performed by the reviewing pathologist, but the signed statement from the pathologist on the histopathology findings is not included. Since this is a pivotal study and the only toxicity study conducted by the sponsor, the complete information is required for review and recommendation for approval and will be requested from the sponsor. |
| 4) Are all necessary and appropriate studies for this agent, ncluding special studies/data requested by the Division during pre-submission communications/ discussions, completed and submitted in this NDA? Please itemize the critical studies ncluded and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity) | Yes | | The Firm has conducted one 28-day bridging toxicity study in rats with their drug product and the listed drug Livalo, with a 14-day recovery period, as requested.<br><br>We also recommended that potentially genotoxic impurities and degradation products may be present in this new Pitavastatin magnesium drug product which may necessitate additional nonclinical qualification per ICH-Q3A and ICH-Q3B.<br><br>However, no gene-toxicity studies have been conducted by the sponsor with their product to qualify the impurities. The sponsor states that no structural alerts were found for Ames TA100 by QSAR method (Toxtfree) in the CMC section. |

| TEM | YES | NO | COMMENT |
|---|---|---|---|
| 5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)? | Yes | | The original application of the reference product was approved in 2009 and all non-clinical studies conducted have been reviewed under the NDA 22-363 (Pitavastatin calcium/Livalo). |
| 6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the mpurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (i.e., adequate repeat studies using the marketed product and/or adequate ustification for why such repetition would not be necessary)? | Yes | | The 28-day bridging toxicity study has been provided, however gene-toxicity studies recommended by us have not been provided. Note that the acceptability of the above toxicity study and qualification of impurities /degradation products in the drug product will be a review issue. |
| 7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route? | Yes | | The route of administration is oral in toxicity studies, as was for the initial application of the LD Pitavastatin calcium (NDA 22-363) and it is also for oral use in the current application, which s the intended route in humans. |
| 8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels? | Yes | | Yes, the draft labeling submitted in general is in accordance with 21 CFR abeling; it is similar to the approved Pitavastatin calcium label, and data is expressed as human dose multiples in mg/m2 (body surface area). |

| TEM | YES | NO | COMMENT |
|---|---|---|---|
| 9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not. | yes | | The application is fileable. Since the recommended bridging toxicology study s provided in the current application. However, the summary Tables are not well presented including the pivotal gross/ histopathology table which lacks severity scores.<br><br>The acceptability of the 28-day toxicity study will be assessed, following review of the data. Additionally, we will examine if there are supportive data to qualify the impurities/ excipients/ degradants in their drug product, since the recommended gene-toxicity studies have not been conducted by the sponsor.<br><br>The sponsor states that "no structural alerts were found for Ames TA100 by QSAR method (Toxfree); hence it was concluded that none of the impurities shows Genotoxicity (as per the agency's guidance: Genotoxic and carcinogenic mpurities in drug substance and products: Recommended Approaches-December 2008". However, no data-sets on QSAR are provided.<br><br>n the current application, the following two *bioequivalence (BE) studies have been conducted*<br>*1. A single-dose fasting bioequivalence (BE) study comparing Pitavastatin 4 mg (Magnesium salt) against Livalo (Pitavastatin) 4 mg (Calcium salt)*<br>*2. A single-dose food-effect study comparing Pitavastatin magnesium 4 mg under fasting and fed conditions.*<br><br>The above BE studies will be reviewed by the Clinical Pharmacology reviewer. |

Reasons for refusal to file: N/A

The following need to be communicated to the sponsor:

1. Please provide a clean copy of the 28-day toxicology study in rats (not marked (b) (4) across every page).
2. Separate detailed gross and histopathology summary Tables, which include the severity scores in the histopathology Tables, are required.
3. You need to submit the signed statement from the reviewing pathologist on the summary of histopathology findings.
4. Please provide details on qualification of all the impurities in the drug product in the pharmacology/toxicology section of your NDA application, since the genetic toxicity studies have not been conducted with your formulation. Please include the levels of impurities in your drug product and the levels qualified in the rat bridging toxicity study.
5. Please provide details on QSAR method used (Toxfree), i.e. submit actual data Tables, drug lot numbers, purity of the tested agents etc. so we may determine the validity of these QSAR methods (Ames TA100 by QSAR method)

Reviewing Pharmacologist: Indra Antonipillai

Supervisory Pharmacologist: Stephanie Leuenroth-Quinn,

File name: 208379-filing.

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INDRA ANTONIPILLAI

05/11/2015

From the pharmacology/toxicology point of view, this application is fileable. Please note that the comments on page 6 need to be communicated to the sponsor.

STEPHANIE J QUINN

05/11/2015