CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

CLINICAL REVIEW(S)

Medical Officer 505(b)(2) NDA Resubmission Review
Division of Metabolism and Endocrinology Products

NDA – 208379
Name of drug – Zypitamag (Pitavastatin magnesium)
Applicant – Zydus Pharmaceuticals, Inc.
Date of Submission – January 17, 2017
Supporting Documents - #14 - 19
PDUFA Goal Date – July 17, 2017
Medical Reviewer – Mary D. Roberts, M.D.

SUMMARY:

This is a Class 2 Resubmission for approval of Zypitamag (pitavastatin magnesium) in dosage strengths of 1, 2, 4 mg for the treatment of primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, LDL-C, apoB, TG and to increase HDL-C by establishing bioequivalence to Livalo (pitavastatin calcium) which was approved under NDA 22363 on August 3, 2009.

In the initial application cycle, the applicant established bioequivalence between Zypitamag and Livalo. There were no clinical or non-clinical deficiencies. However, the Office of Pharmaceutical Quality (OPQ) recommended a complete response due to deficiencies at the manufacturing facility. A Complete Response Letter was issued January 26, 2016.

The applicant, with this current Class 2 resubmission, has addressed the deficiencies and has undergone an inspection of the manufacturing facility, which resulted in a No Action Indicated classification. The OPQ review team now recommends approval. No new pharmacology/toxicology, clinical pharmacology, or clinical information has been submitted to the application. The establishment of bioequivalence still holds per the review of the biopharmaceutical review team. Routine pharmacoviligance practices have not revealed a safety concern which would change the risk-benefit profile for this pitavastatin product.

Clinical review recommends tentative approval of this product.

BIOEQUIVALENCE STUDIES/SAFETY:

No new clinical or clinical pharmacology information has been submitted to the NDA since issuance of the CR letter.

In the initial application the applicant established bioequivalence to Livalo at the highest dose, 4 mg, in two studies – a bioavailability study and food effect study – and has received a biowaiver for the lower doses. For further details, please refer to the original clinical pharmacology and biopharmaceutical review of this application. Review of the efficacy and safety of the listed drug as well as consideration of the safety of the magnesium salt did not reveal new safety signals that would change the risk-benefit

assessment of this product. Please see the original review of the NDA for further information.

CMC:
In the previous review cycle, the Office of Pharmaceutical Quality recommended a Complete Response due to numerous cGMP deficiencies identified during inspection of the proposed drug product manufacturer.

In this current review cycle, the OPQ review team recommends approval, including the Overall Manufacturing Inspection Recommendation dated May 8, 2017. An inspection of the drug product manufacturer was completed on February 16, 2017 and resulted in a No Action Indicated Classification. Please see the OPQ review team's review for more details.

PEDIATRIC STUDY REQUIREMENTS:
The indications for primary and mixed dyslipidemia sought after by the applicant in the original 505b2 NDA submission were reviewed by the PeRC committee during the first review cycle on November 18, 2015. These indications were granted a full waiver because studies are impossible or highly impractical. Please see original NDA review for further details.

LABELING:
In the resubmission, draft labeling was proposed and reviewed. A DPMH consult was requested to review the PLLR format of the labeling. The DPMH review team suggested minor edits to Section 8 of labelling which were conveyed to the sponsor.

At the completion of this review, labeling negotiations were underway between the Agency and the applicant.

DMEPA has reviewed the Zypitamag prescribing information, carton and container packaging and has determined they are acceptable from a medication error perspective.

RECOMMENDATION
After review of the applicant's submitted patent and exclusivity documents, the 505(b)(2) committee determined this application is eligible for a tentative approval.

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/s/

MARY D ROBERTS
06/21/2017

JAMES P SMITH
06/21/2017

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

NDA – 208379

Name of drug – Zypitamag Tablets (pitavastatin magnesium)

Applicant – Zydus Pharmaceuticals/ Cadila Healthcare Limited, India

Date of Submission – March 31, 2015

PDUFA Goal Date – January 31, 2016

Medical Reviewer – Mary D. Roberts, M.D.

Zydus Pharmaceuticals has submitted a 505(b)(2) New Drug Application (NDA) for its formulation of pitavastatin using a magnesium salt (pitavastatin magnesium) in dosage strengths of 1, 2, and 4 mg for the treatment of primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, LDL-C, apoB, TG and to increase HDL-C to the Division on March 31, 2015. The applicant is relying on the published literature and FDA's safety and efficacy findings for the Reference Listed Drug (RLD), Livalo® (pitavastatin calcium), along with the results of two clinical bioequivalence studies. Livalo® manufactured by Kowa Pharmaceuticals, Inc., was approved under NDA 22363 on August 3, 2009.

Drug in study

The drug product is pitavastatin magnesium tablets 1 mg, 2 mg, and 4 mg, referred to in this document as PitavaMg. Pitavastatin acts by competitively blocking the HMG-CoA reductase enzyme. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonic acid, a critical step in cholesterol biosynthesis. Therefore inhibition of HMG-CoA's enzymatic action by pitavastatin reduces cholesterol formation in the liver and results in up-regulation of LDL receptors which transports LDL-C from the blood into the liver, lowering LDL-C values in the bloodstream.

Regulatory history

- 23 November 2012, the applicant requested guidance for their proposed 505(b)(2) application for pitavastatin magnesium.
- 12 February 2013, a pre-IND file was opened for this product and the applicant was advised to submit a briefing document regarding the proposed development plan with questions for the Division.
- Written responses dated 15 April 2013, were sent to the applicant recommending two studies for the 505(b)(2) application: (a) a single-dose fasting bioequivalence study

comparing pitavastatin magnesium 4 mg (test) against pitavastatin calcium 4 mg (reference), and (b) a single-dose food-effect study comparing pitavastatin magnesium 4 mg under fasting (reference) and fed (test) conditions. Questions regarding biowaivers for the lower doses of pitavastatin magnesium tablets and dissolution studies were addressed. Due to limited CMC information provided, the CMC review team referred the applicant to several published CMC guidelines. The Division requested a summary of safety for pitavastatin be included in a NDA submission using information from the applicant's studies, available published literature, databases, and labeled safety information from the reference listed drug.

- On 31 May 2013, the applicant submitted IND 117674 for pitavastatin magnesium for the treatment of primary hyperlipidemia and mixed dyslipidemia. The IND included protocols for two bioavailability study protocols and a bridging nonclinical toxicology study. The applicant was informed in letters dated 30 July 2013 and 22 November 2013 that the bridging non-clinical toxicity study should use the reference listed product, Livalo®, instead of the applicant's formulation of the pitavastatin calcium product.
- On 11 July 2014, the applicant submitted a Type C meeting request to discuss the Division's expectations on the pharmacology/toxicology requirements, genotoxic assessments, pediatric assessments, clinical studies, and labeling requirements for a proposed 505(b)(2) marketing application. This request was granted with written responses in lieu of a meeting. The Division's written responses were sent to the applicant on 22 September 2014. In addition to guidance regarding CMC and biopharmaceutical requirements, the applicant was informed a waiver for a non-clinical bridging toxicity study using PitavaMg and the RLD, Livalo® would not be granted. They were also advised to include a review of the efficacy and safety of Livalo® utilizing available literature and databases, include information regarding the safety of magnesium in the future NDA submission, and submit an initial Pediatric Study Plan in accordance with PREA and FDASIA requirements.

Biopharmaceutical Studies Submitted to NDA 208379

- BA1386248 – Single-dose bioequivalence study under fasting conditions
- BA1386249– Single-dose bioequivalence study under fed and fasted conditions

These studies were reviewed in detail by Dr. Johnny Lau from the Office of Clinical Pharmacology. The clinical pharmacology review team recommends approval of this product. Please see Dr. Lau's review for further details.

Zydus Pharmaceuticals has submitted debarment certification for both of these studies.

STUDY SUMMARIES

BA1386248

This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover, bioequivalence (BE) study of PitavaMg 4 mg tablet and Livalo® 4 mg tablets. Treatments were administered under fasting conditions to 28 (27 completed)

healthy Asian men. Patients fasted for at least 10 hours before dosing and at least 4 hours post-dose in each period. The interval between dosing periods was at least 7 days.

Table 1: PitavaMg PK parameters from the pivotal fasting BE study BA1386248

Rosuvastatin Pharmacokinetic Parameters	Geometric Mean		Ratio (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
C_{max}	123.111	110.181	111.74	102.55	121.74
AUC_t	357.655	340.252	105.11	100.36	110.09
AUC_{inf}	371.574	356.173	104.32	99.20	109.71

As shown in Table 1, the 90% confidence interval for the geometric mean ratio of the BE metrics between test and reference products were within the prespecified bounds of 80% -125%. Therefore, PitavaMg 4 mg was bioequivalent to Livalo® 4 mg under fasting conditions.

Demographics
A total of 28 healthy Asian men were randomized. The mean age was 28 years (range 20-42 years), BMI was 21.3 kg/m^2 (range 18.7 -26.9 kg/m^2).

Safety
Volunteers were queried about adverse events (AE) during clinical examinations, during vital sign recordings, and 16, 24, 36, and 48 hours post-dose. Blood samples for safety assessments included a complete blood count, chemistry profile (with Magnesium), CK, and TSH were taken at the time of screening and at the end of the study. At the beginning of the second treatment period, serum CK, creatinine, and Mg were collected. Patients with clinically significant abnormalities in these laboratories prior to the second treatment period were not allowed to continue.

No serious adverse events (AE) were reported. A total of 3 adverse events were reported "headache", "blood glucose increased", "gastritis". The last AE resulted in study discontinuation. This discontinuation occurred in 28 year old man who received one 4 mg dose of Livalo® at the beginning of the first dosing period. Ten days later the patient complained of epigastric abdominal pain (adverse event of "gastritis") without nausea or vomiting. The patient was given ranitidine, dicyclomine HCL, and paracetamol for 3 days and was discontinued from the study before the second dosing period. The other AEs were headache rated as mild, resolved within an hour without intervention and blood glucose increased. The AE of "blood glucose increased" occurred in a 38 year old man, BMI 22.9 kg/m^2, with a baseline glucose value of 92.4 mg/dL, urinalysis at screening showed 2+ glucose, a repeat urinalysis 3 days later was negative. He completed the study without incident. A non-fasting blood glucose level at the end of the study was 182.9 mg/dL, a repeat non-fasting glucose the following day was 110.9 mg/dL. The case report

states, "subject's end study clinical examination was normal. Subject has no complaint. He is feeling fine. His random glucose is WNL. No need to further follow-up."

Reviewer comment: Statin therapy has been associated with elevations in blood glucose and HbA1c, and in some cases new onset type 2 diabetes. This patient had an abnormal urinalysis, which cleared prior to dosing, but suggests that at baseline, this patient may have had abnormalities in glucose homeostasis.

After review of the clinical laboratory data, no other subjects demonstrated clinically significant laboratory changes. There were no instances of CK>3x ULN, ALT > 3x ULN, AST >2xULN, or levels of magnesium outside of normal limits.

BA1386249 – Food Effect study

This was an open-label, single-dose, randomized, two-period, two-sequence, two-treatment, crossover, food effect bioavailability study using PitavaMg 4 mg tablets. A single dose of PitavaMg 4 mg was administered under fed (high fat/calorie meal) and fasting conditions to 28 healthy Asian men.

Table 2: PitavaMg PK parameters from the pivotal fed BA study BA1386249

Pitavastatin Pharmacokinetic Parameters	Geometric Mean		Ratio (Fed/Fasting)	90% Confidence Interval	
	Fasting	Fed		Lower	Upper
C_{max}	155.097	95.270	61.43	55.80	67.61
AUC_t	405.387	384.695	94.90	91.42	98.50
AUC_{inf}	422.006	398.626	94.46	91.04	98.01

As shown in Table 2, the 90% confidence interval for the geometric mean ratio under fed and fasted conditions for pitavastatin AUC ratios are within the prespecified bounds of 80% -125%, whereas the pitavastatin Cmax ratio is not. According to the clinical pharmacology review team, the results indicate that there is statistically significant food effect for the PitavaMg that is consistent with the RLD, Livalo®, which exhibited a 43% decrease in Cmax but no difference in AUC in fed versus fasted conditions. It appears that the Livalo® food effect was not considered clinically meaningful during the review of the RLD application as the label states Livalo® may be taken with or without food. The clinical pharmacology review team does not recommend any changes to the RLD or PitavaMg label regarding these findings.

Demographics

A total of 28 healthy Asian men were randomized. The mean age was 30 years (range 18-43 years), BMI was 21.8 kg/m^2 (range 18.6 -26.5 kg/m^2).

Safety

Volunteers were queried about adverse events (AE) during clinical examinations, during vital sign recordings, and 16, 24, 36, and 48 hours post-dose. Blood samples for safety assessments included a complete blood count, chemistry profile (with Magnesium and liver transaminases), CK, and TSH were taken at the time of screening and at the end of the study. At the beginning of the second treatment period, only serum CK, creatinine, and Mg were collected. Patients with clinically significant abnormalities in these laboratories prior to the second treatment period were not allowed to continue.

No serious adverse events or discontinuations due to adverse events were reported during the conduct of this study. One subject experienced an adverse event reported as "ALT increased". This event occurred in a 20 year old Asian man. Prior to the first dose of Livalo® 4 mg his laboratory values were unremarkable: ALT was 27.5 U/L (reference range 4.8 – 55.4), AST 25.3 U/L (15.7 – 46.4), total bilirubin 0.5 mg/dL (0.2 -1.2), alkaline phosphatase 92 U/L (42.0 – 124.3). As per the protocol, no additional liver transaminases were obtained until the end of the study. At that time, [approximately 2 weeks following the first dose of PitavaMg 4 mg (fed state) in the first period, and two days after the PitavaMg 4 mg (fasted state) in the second period], the patient's ALT and AST had increased from baseline (ALT 130 U/L which was 2x ULN, AST 80.5 U/L which was 1.7x ULN). Total bilirubin 0.4 mg/dL and alkaline phosphatase 106.5 U/L were essentially unchanged from baseline. A follow-up ALT 3 days later was 86.5 U/L, which was considered by the investigator to not be clinically significant as the ALT had decreased and the patient was asymptomatic and physical exam was normal without icterus. There was no further follow-up.

Reviewer comment: Elevations in liver transaminases is a well-known side effect of statin therapy, including pitavastatin. This case does not meet the biochemical definition of Hy's Law. There were no other patients with elevations in liver transaminases beyond the upper limit of normal. The label for pitavastatin adequately characterizes this safety concern.

Magnesium salt
The amount of magnesium present in a 4 mg PitavMg tablet is approximately (b) (4) 106 mg.

The current recommended dietary allowance (RDA) for magnesium by age is listed below.[1]

Table 3: RDAs for magnesium

Age	Male	Female	Pregnant	Lactating
0-6 months	30 mg*	30 mg*		
7-12 months	75 mg*	75 mg*		
1-3 years	80 mg	80 mg		
4-8 years	130 mg	130 mg		
9-13 years	240 mg	240 mg		
14-18 years	410 mg	360 mg	400 mg	360 mg
19-30 years	400 mg	310 mg	350 mg	310 mg
31-50 years	420 mg	320 mg	360 mg	320 mg
51+ years	420 mg	320 mg		

*Adequate intake

The following table lists the tolerable upper intake levels for magnesium[2]
Since no evidence suggests magnesium when ingested from foods is associated with adverse events, the tolerable upper intake values in the table below are derived from adverse effects that were obtained from pharmacological use of supplemental magnesium.

Table 4: Tolerable upper intake levels for magnesium from non-food sources[a]

Age	Amount of supplementary Mg
0-12 months	Not established
1-3 years	65 mg (2.7 mmol)
4-8 years	110 mg (4.6 mmol)
8 years-adults	350 mg (14.6 mmol)

[a]The UL for magnesium represents intake from pharmacological agents only and does not include intake from food and water

According to the Institute of Medicine (IOM), Food and Nutrition Board, the safe tolerable upper limit for daily ingestion of supplementary magnesium from non-food sources in children greater than 8 years of age through adulthood is 350 mg/day.

This upper limit was based on the primary initial manifestation of excessive magnesium intake as diarrhea. The following is taken directly from the IOM's report.

[1] Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium, Phaosphorus, Magnesium, Vitamin D, and Fluoride. Washington,DC: National Academies Press, 1997.
[2] Ibid.

Gastrointestinal symptoms, including diarrhea, developed in 6 of 21 patients (51- to 70-year-old males and females) receiving long-term magnesium chloride therapy at levels of 360 mg (15 mmol) of magnesium (Bashir et al., 1993). Gastrointestinal manifestations developed in 5 of 25 pregnant women being given 384 mg (16 mmol) of daily magnesium as magnesium chloride supplements for the prevention of preterm delivery, although one patient receiving the placebo treatment also developed diarrhea (Ricci et al., 1991). Diarrhea was also noted in 18 of 50 healthy white and black men and women (aged 31 through 50 years) who were ingesting 470 mg (19.6 mmol) of magnesium as magnesium oxide daily (Marken et al., 1989). Levels of fecal output of soluble magnesium and fecal magnesium concentration were elevated in individuals with diarrhea induced by 168 to 2,320 mg (7 to 97 mmol) of magnesium as magnesium hydroxide (Fine et al., 1991b).

However, other studies using similar or even higher levels of supplemental magnesium reported no diarrhea or other gastrointestinal complaints. Healthy 18- to 38-year-old males given diets enriched with magnesium oxide at levels up to 452 mg (18.9 mmol) daily for 6 days did not report the occurrence of any gastrointestinal symptoms (Altura et al., 1994). This study of the effect of magnesium-enriched diets on absorption involved the fortification of foods with magnesium, which may have different effects from the administration of magnesium supplements outside the normal diet. Furthermore, no diarrhea was reported in patients of varying ages receiving an average of 576 mg (24 mmol)/day of supplemental magnesium as magnesium oxide in a metabolic balance study for 28 days (Spencer et al., 1994). Diarrhea or other gastrointestinal complaints were not observed in patients receiving up to 1,200 mg (50 mmol) of magnesium in the form of an aluminum-magnesium-hydroxycarbonate antacid over a 6-week trial period (Nagy et al., 1988). In a longer-term study, a group of postmenopausal women received daily supplements of 226 to 678 mg (9.4 to 28.3 mmol) of magnesium as magnesium hydroxide for 6 months followed by 226 mg (9.4 mmol) of magnesium for 18 months without any observations of gastrointestinal complaints (Stendig-Lindberg et al., 1993). Diabetics were supplemented with 400 mg (16.7 mmol) of magnesium daily for 8 weeks in the form of magnesium oxide or magnesium chloride without any gastrointestinal complications (Nadler et al., 1992). Elderly subjects supplemented with 372 mg (15.5 mmol) of magnesium daily over a 4-week period did not report any diarrheal effects or other gastrointestinal complaints (Paolisso et al., 1992).

Reviewer comment: The amount of magnesium in the 4 mg pitavastatin magnesium tablet is (b) (4) *106 mg and substantially under the 350 mg tolerable upper intake levels advised by the IOM.*

AUDITS

The Division of New Drug Bioequivalence Evaluation within the Office of Study Integrity and Surveillance (OSIS) recommended accepting the data without an on-site inspection. The analytical and clinical sites, (b) (4) had been inspected on (b) (4) and received a No Action Indicated (NAI) classification. According to OSIS, the timeframe when the inspection occurred overlapped when the studies in this application were conducted.

CMC

The chemistry/manufacturing and controls team recommend a complete response due to manufacturing facility deficiencies. At the time of the clinical review's completion, the CMC final review recommendations are pending.

PHARMACOLOGY/TOXICOLOGY

The pharmacology/toxicology review team recommends approval of this product. A 4-week bridging toxicity study in rats utilizing PitavaMg and the RLD did not show toxicological meaningful differences between PitavaMg and Livalo®. According to the review team this study provided an adequate bridge to the Division's prior approval decision for the RLD, Livalo®. No changes to the pharmacology/toxicology sections of labeling are recommended. Please see Dr. Indra Antonipillai's review for further details.

FINANCIAL DISCLOSURE

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

LABELING

As this application will be granted a complete response, no approved labeling will be attached to this action.

With resubmission, the applicant will need to resubmit labeling which omits all information related to indications which are protected under patent/exclusivity regulations and reflects the most updated version of the Livalo® label.

PROPRIETARY NAME

The applicant proposed to use the name Zypitamag which was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) and was determined to be acceptable.

PEDIATRIC STUDY REQUIREMENTS

The applicant did not include an initial pediatric study plan (iPSP), an agreed iPSP, or a pediatric assessment in this submission, although they had been previously advised of the requirement to submit an iPSP prior to submission of their NDA in Type C written responses dated 22 September 2014. With the NDA submission, the applicant requested a full pediatric waiver for PitavaMg based on the following justification:

- The Reference Listed Drug, Livalo® (pitavastatin calcium) under NDA 22363 was reviewed by PeRC in April 2009 and was granted a full waiver for pediatric studies based on a lack of meaningful therapeutic benefit over existing therapies for pediatric patients.

The Division of Pediatric and Maternal Health (DPMH) was consulted to determine if the lack of an agreed iPSP should be sole grounds for a Refuse-to-File (RTF) action for this application. DPMH concluded that this omission should not be the only basis for a RTF action, because the applicant stated their intention to seek full waivers for pediatric assessments under PREA in a Type C meeting prior to NDA submission; DMEP has granted full waivers for pediatric assessments under PREA for products in the same class for the same indication as this product; and, finally, DMEP agrees that a full waiver for pediatric assessments under PREA would be appropriate for this product at this time.

The PitavaMg application was reviewed by the PeRC PREA subcommittee on 18 November 2015 and was granted a full waiver for pediatric studies because studies are impossible or highly impractical. Dyslipidemic patterns in children are frequently associated with obesity and characterized by increased TG and decreased HDL-C, and normal to modestly elevated LDL-C, which is a different pattern than that observed in adult patients with primary hyperlipidemia or mixed dyslipidemia in which LDL-C is elevated. Pharmacologic treatment in children is rarely indicated; recommended first-line therapy focuses on behavioral and lifestyle modifications. These factors contribute to pediatric trials for this treatment indication as being impossible or highly impractical.

RECOMMENDATION

No deficiencies were noted in the clinical review of this product. PitavaMg 4 mg was well tolerated and was consistent with the known safety profile of the reference listed drug, Livalo®; however, due to issues with the manufacturing facility for this product, this reviewer recommends a complete response and defers to the CMC review team for input on how the applicant may address deficiencies in the NDA.

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/s/

MARY D ROBERTS
01/13/2016

JAMES P SMITH
01/13/2016

Clinical Filing Review Addendum

NDA 208379
Applicant: Zydus Pharmaceuticals
Drug: pitavastatin tablets, 1 mg, 2 mg, and 4 mg (magnesium salt)
Date of Addendum: 29 May 2015
Reviewer: James P. Smith, MD, MS

In my 25 May 2015 clinical filing review, I concluded that the clinical section of the application was not fileable. This addendum reverses that recommendation and explains the rationale.

Specifically, I cited the following two deficiencies:

1. *The applicant failed to submit an initial pediatric study plan (iPSP). In 22 September 2014 written responses, the Division responded to the question "Based on the information presented in the background section of Pediatric assessment, Zydus is requesting waiver for pediatric assessment study," with "The Agency will consider your waiver request in the context of reviewing your complete initial Pediatric Study Plan submission. See Section 3.0 below, PREA Requirements, for additional information."*

2. *The applicant did not submit datasets (case report tabulations) as required by 21 CFR 314.50(f)(1). At a minimum, the applicant must submit datasets that contain the raw data for demographics, treatment allocation, exposure, laboratory data, adverse events, and vital signs. Dates of collection of safety data and dates of drug administration must be included, as well as dates of all scheduled and unscheduled study visits.*

The Division had been communicating with the Division of Pediatric and Maternal Health (DPMH) early in the filing period regarding the applicant's failure to submit an iPSP, and it was our understanding that this was a basis for an RTF action. Upon further discussion with Dr. Lynne Yao (Acting Director, Division of Pediatric and Maternal Health) today, however, we have determined that this should not be the basis for an RTF action for this application. The listed drug, Livalo, was approved relatively recently (August 2009) and as stated in the approval letter, we waived the pediatric study requirement for that application because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. Given that the current application does not seem to present any unique considerations for pediatric patients (e.g., a different formulation), it is highly likely that we would waive the pediatric study requirement for this product as well, if approved.

Regarding the second deficiency, the Division held a teleconference with the sponsor today to determine whether they would be able to submit datasets in a timely fashion. Following the phone call, a written information request was sent via email regarding the dataset needs to facilitate this review. The sponsor confirmed, via email, that "in couple of weeks' time we will be able to provide the requested data as discussed" (see DARRTS ID 3770083). With this commitment, I have concluded that it is acceptable to file this NDA.

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/s/

JAMES P SMITH
05/29/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: NDA 208379 **Applicant: Zydus Pharm.** **Stamp Date: 31 March 2015**

Drug Name: pitavastatin tablets, 1 mg, 2 mg, and 4 mg (magnesium salt) **NDA Type: 505(b)(2)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Module 2.5 (Clinical Overview) is adequate
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Livalo (NDA 22363)
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)				Single-dose fasting BE study; Single-dose food-effect study; 4-week bridging toxicology study
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title:			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: Arms: Location in submission:				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: BA1386248-01, an open-label, randomized, 2-period, 2-treatment, 2-sequence, crossover, balanced, single-dose oral BE study of pitavastatin tablets 4 mg vs. Livalo tablets 4 mg in health adult human subjects under fasting conditions. Pivotal Study #2: BA1386249-01, an open-label, randomized, 2-period, 2-treatment (fed vs. fasting), 2-sequence, crossover, balanced, single-dose food effect BA study of pitavastatin tablets 4 mg in healthy adult human subjects under fasting and fed conditions	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Module 2.5 is adequate
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		Only 4 AEs reported across both clinical studies; coding dictionary not necessary for review
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		The applicant never submitted an initial PSP prior to NDA submission. In 22 Sept 2014 Type C written responses, Zydus stated their intent to request a waiver for pediatric assessment. The division responded, "The Agency will consider your waiver request in the context of reviewing your complete initial Pediatric Study Plan submission. See Section 3.0 below, PREA Requirements, for additional information."
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S.		X		

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	population?				
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			The only datasets submitted include information re: drug concentration and PK.
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			Clin pharm to review
37.	Are all datasets to support the critical safety analyses available and complete?		X		Tabulation datasets to support safety analyses were not submitted.
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	CRFs appear to have been submitted for all trial participants
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Module 1.3.4
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			See individual CSRs

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? No

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

1. The applicant failed to submit an initial pediatric study plan (iPSP). In 22 September 2014 written responses, the Division responded to the question "Based on the information presented in the background section of Pediatric assessment, Zydus is requesting waiver for pediatric assessment study," with "The Agency will consider your waiver request in the context of reviewing your complete initial Pediatric Study Plan submission. See Section 3.0 below, PREA Requirements, for additional information."

2. The applicant did not submit datasets (case report tabulations) as required by 21 CFR 314.50(f)(1). At a minimum, the applicant must submit datasets that contain the raw data for demographics, treatment allocation, exposure, laboratory data, adverse events, and vital signs. Dates of collection of safety data and dates of drug administration must be included, as well as dates of all scheduled and unscheduled study visits.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

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

/s/

JAMES P SMITH
05/25/2015