CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	208379
Applicant	Zydus Pharmaceuticals (USA) Inc.
Date of Submission	17 January 2017
PDUFA Goal Date	17 July 2017
Proprietary Name / Established (USAN) names	ZYPITAMAG / pitavastatin
Dosage forms / Strength	1 mg, 2 mg, and 4 mg tablets
Proposed Indication	**Primary Hyperlipidemia and Mixed Dyslipidemia** Adjunctive therapy to diet to reduce elevated total cholesterol, LDL-C, Apo B, TG, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia
Recommended:	Approval

Material Reviewed/Consulted & Primary Reviewer(s)		
OPQ Review	10 May 2017	Suong Tran, PhD (Team Lead); See review for listing of quality review team
Medical Officer Review	21 Jun 2017	Mary Roberts, MD
Pharmacology/Toxicology Review	24 Apr 2017	Indra Antonipillai, PhD
Maternal Health Review (PLLR Labeling)	22 Jun 2017	Carrie Ceresa, PharmD, MPH
OSE/DMEPA Label & Labeling Review	03 Apr 2017	Casmir Ogbonna, PharmD, MBA
OSE/DMEPA Proprietary Name Review	26 Apr 2017	Casmir Ogbonna, PharmD, MBA
OPDP Labeling Review	07 Jul 2017	Ankur Kalola, PharmD

CMC: Chemistry, Manufacturing, and Controls; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion

The applicant is seeking approval of pitavastatin tablets (magnesium salt) for primary hyperlipidemia and mixed dyslipidemia via the 505(b)(2) regulatory pathway, relying on the Agency's previous determination of safety and effectiveness for Livalo (pitavastatin tablets, calcium salt), which was approved on 03 August 2009 (NDA 22363). This is a class 2 resubmission following a Complete Response (CR) dated 26 January 2016.

See my 25 January 2016 summary review for details regarding this application. The CR action during the first cycle was a result of a recommendation from the Office of Pharmaceutical Quality. The proposed drug product manufacturer (Cadila Healthcare Limited, located at Sarkhej-Bavla NH No. 8A Maraiya, Taluka: Sanand, Ahmedabad, Gujurat, India) was inspected in September 2014 as a site-wide surveillance coverage and numerous cGMP deficiencies related to the manufacture of solid oral dosage form products were identified. With this resubmission, OPQ notes that the most recent inspection of this manufacturer (completed on 16 February 2017) resulted in a No Action Indicated classification; in turn, OPQ now recommends approval of this application.

Labeling has been reviewed by the review team, including a review of PLLR labeling by the Division of Pediatrics & Maternal Health, and has been found acceptable.

On 08 June 2017, we requested any updates on patent litigation that had changed since the resubmission of this application. On 11 July 2017, the sponsor submitted a patent amendment to inform the Agency that the plaintiffs have requested the court to dismiss the action without prejudice, as the only relevant patent expired on 20 December 2016. On 14 July 2017, the sponsor submitted another amendment to inform the Agency that the U.S. District Court for the Southern District of New York has granted the motion to dismiss. The 505(b)(2) committee has determined that this application could now receive an approval action instead of the previously anticipated tentative approval.

Discussion / Regulatory Recommendation

The applicant has satisfactorily responded to the 26 January 2016 complete response letter. I concur with the recommendations from all reviewers to approve this application.

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/s/

JAMES P SMITH
07/14/2017

Summary Review for Regulatory Action

Date	*See electronic stamp*
From	James P. Smith, MD, MS
Subject	Summary Review for Regulatory Action
NDA#	208379
Applicant	Zydus Pharmaceuticals (USA) Inc.
Date of Submission	31 March 2015
PDUFA Goal Date	31 January 2016
Proprietary Name / Established (USAN) names	ZYPITAMAG / pitavastatin
Dosage forms / Strength	1 mg, 2 mg, and 4 mg tablets
Proposed Indication	**Primary Hyperlipidemia and Mixed Dyslipidemia** Adjunctive therapy to diet to reduce elevated total cholesterol, LDL-C, Apo B, TG, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia
Recommended:	Complete response

Material Reviewed/Consulted & Primary Reviewer(s)		
Clinical Pharmacology Review	09 Dec 2015	S.W. Johnny Lau, RPh, PhD
OPQ Review	21 Dec 2015	Suong Tran, PhD (Team Lead); See review for listing of quality review team
Medical Officer Review	13 Jan 2016	Mary Roberts, MD
Pharmacology/Toxicology Review	24 Nov 2015	Indra Antonipillai, PhD
OSIS Memo	27 Aug 2015	Shila S. Nkah
OSE/DMEPA Label & Labeling Review	29 Oct 2015	Leeza Rahimi, PharmD
OSE/DMEPA Proprietary Name Review	10 Dec 2015	Leeza Rahimi, PharmD

CMC: Chemistry, Manufacturing, and Controls; OSIS: Office of Study Integrity and Surveillance; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis

The applicant is seeking approval of pitavastatin tablets (magnesium salt) for primary hyperlipidemia and mixed dyslipidemia via the 505(b)(2) regulatory pathway, relying on the Agency's previous determination of safety and effectiveness for Livalo (pitavastatin tablets, calcium salt), which was approved on 03 August 2009 (NDA 22363).

Dr. S.W. Johnny Lau reviewed the results of the two clinical pharmacology studies (BA1386248 [Study 248] and BA1386249 [Study 249]) submitted to support approval. Study 248 assessed the relative bioavailability between the 4 mg pitavastatin tablet (magnesium salt) of the to-be-marketed product with the 4 mg tablet of US-manufactured Livalo; Dr. Lau concludes that these products are bioequivalent. Study 249 assessed the food effect on the bioavailability of the 4 mg pitavastatin tablet (magnesium salt). This study shows that a high-fat meal decreases pitavastatin C_{max} and AUC by 38.6% and approximately 5%, respectively; Dr. Lau concludes that this decrease in pitavastatin AUC is not significant. See his review for complete details. The Office of Clinical Pharmacology recommends approval; I concur that there are no issues related to clinical pharmacology that would preclude approval.

The applicant requested a biowaiver for the 1 mg and 2 mg pitavastatin tablets. The biopharmaceutics reviewer found that the comparative dissolution profiles of pitavastatin 1 mg and 2 mg tablets (magnesium salt) are similar to that of the 4 mg tablet; therefore, a waiver is granted from a biopharmaceutics perspective under 21 CFR 320.22(d)(2). (The biopharmaceutics reviewer does recommend a revision to their dissolution specification from NLT (b) (4)% (Q) in (b) (4) minutes.)

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for a complete response. Specifically, the proposed drug product manufacturer (Cadila Healthcare Limited, located at Sarkhej-Bavla NH No. 8A Maraiya, Taluka: Sanand, Ahmedabad, Gujurat, India) was inspected in September 2014 as a site-wide surveillance coverage and numerous cGMP deficiencies related to the manufacture of solid oral dosage form products were identified. According to the OPQ review, a 483 was issued and a warning letter is currently under review in the Office of Compliance.

Dr. Indra Antonipillai reviewed this application from the pharmacology/toxicology perspective. The applicant conducted a 28-day bridging toxicity study in rats with their product and Livalo, followed by a 14-day drug-free recovery period. No toxicological meaningful differences were identified between pitavastatin magnesium and Livalo. The total impurities present in the drug product are qualified. Dr. Antonipillai recommends approval, and I concur that there are no outstanding issues related to pharmacology/toxicology.

Dr. Mary Roberts reviewed this application from the clinical perspective. Among the 28 healthy Asian men in Study 248, a total of 3 adverse events were reported – "Headache," "Blood glucose increased," and "Gastritis" – the latter resulting in discontinuation. There were no serious adverse events in this study. There were no instances of CK >3x ULN, ALT >3x ULN, or AST >2x ULN. Among the 28 healthy Asian men in Study 249, only one AE was reported: "ALT increased." This event occurred in a 20-y/o man who had ALT and AST of 27.5 U/L and 25.3 U/L, respectively, at the screening visit, which was a week prior to first dose. Per protocol, the subject received a single dose of pitavastatin magnesium 4 mg (fed state) and, a week later, received a single dose of pitavastatin magnesium 4 mg (fasting state). Two days after this dose, end-of-study ALT and AST were 130 U/L (2x ULN) and 80.5 U/L, respectively, with normal bilirubin and alkaline phosphatase. A follow-up ALT 3 days later was 86.5 U/L; the patient was asymptomatic. Dr. Roberts concludes that elevations in liver transaminases are a well-known side effect of statin therapy, including pitavastatin, and that the label for pitavastatin adequately characterizes this safety concern. I agree, although I would also note that it is unclear that such a rise in transaminases is related to the drug, as there are a number of factors that could contribute to such a modest rise in ALT. It is reassuring that the 28-day bridging toxicity study did not raise liver-related concerns for the pitavastatin magnesium formulation. Dr. Roberts recommends a complete response on the aforementioned deficiencies with the manufacturing facility, deferring to the CMC review team. She notes no deficiencies in the clinical review of the product; I agree that there are no outstanding clinical issues that would preclude approval.

The applicant requested a full pediatric waiver for this product based on the fact that the listed drug, Livalo, was reviewed by PeRC in April 2009 and granted a full waiver for pediatric studies based on a lack of meaningful therapeutic benefit over existing therapies for pediatric patients. The current application was reviewed by PeRC on 18 November 2015 and was granted a full waiver for pediatric studies because studies are impossible or highly impractical.

The Office of Study Integrity and Surveillance/ Division of New Drug Bioequivalence Evaluation recommended accepting data without on-site inspections because of recent satisfactory inspections of both the analytical and clinical sites ((b) (4) .).

The applicant's proposed propriety name, Zypitamag, was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Labeling was reviewed by DMEPA and recommendations were provided for the carton and container labels to provide additional features to differentiate the three proposed strengths.

Discussion / Regulatory Recommendation

The applicant has demonstrated that the magnesium salt of pitavastatin (Zypitamag) is bioequivalent to the calcium salt of pitavastatin, which is approved as Livalo. There are no clinical or nonclinical deficiencies that would preclude approval. However, the Office of Pharmaceutical Quality recommends a complete response on the basis of deficiencies with regard to the manufacturing facility. Given that there is no pressing public health need for an alternative formulation for pitavastatin, which is one of seven statins marketed in the U.S., I concur with the recommendation not to approve this application until the issues related to the manufacturing facility are resolved.

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/s/

JAMES P SMITH
01/25/2016