CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 208379	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Zypitamag Established/Proper Name: pitavastatin Dosage Form: Tablets Strengths: 1 mg, 2 mg and 4 mg		
Applicant: Zydus Pharmaceuticals (USA) Inc.		
Date of Receipt: 3/31/2015		
PDUFA Goal Date: 1/31/2016	Action Goal Date (if different): July 14, 2017	
RPM: Richard Whitehead		
Proposed Indication(s): Indicated as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.		

GENERAL INFORMATION

a) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

b) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Livalo® (pitavastatin) tablets, 1 mg, 2 mg and 4 mg (NDA 022363)	*FDA's previous finding of safety and effectiveness (e.g., clinical, nonclinical, labeling)*

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

c) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

To establish a "bridge" between proposed drug product (i.e Pitavastatin Tablets, 1 mg, 2 mg and 4 mg (Magnesium Salt)) and RLD (i.e LIVALO (pitavastatin) Tablets, 1mg, 2mg and 4 mg) we have conducted following study.

1. A single-dose fasting bioequivalence study comparing Pitavastatin Tablet 4 mg (Magnesium salt) against Livalo (Pitavastatin) Tablet 4 mg (Calcium salt)

2. A single-dose food-effect study comparing Pitavastatin magnesium 4 mg) under fasting and fed conditions.

3. 4-Weeks Repeated Dose Toxicity Study of Pitavastatin Tablets 4 mg (Magnesium Salt) by Oral Route in Wistar Rats with 2 - Weeks Recovery Period and to compare the toxicity with the reference drug, LIVALO (Pitavastatin) Tablets 4 mg.

RELIANCE ON PUBLISHED LITERATURE

d) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

YES ☒ NO ☐

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☒ NO ☐

Livalo® (Pitavastatin) Tablets, 1 mg, 2 mg and 4 mg (NDA 022363)

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

e) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☒ NO ☐

*If "**NO**," proceed to question #10.*

f) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Livalo® (Pitavastatin) Tablets, 1 mg, 2 mg and 4 mg	NDA 022363	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

g) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

h) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☒

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☒

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☒

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

i) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

New formulation (Change from pitavastatin calcium is currently marketed by Kowa Co., LTD, under NDA 022363 (Livalo) to Pitavastatin (Magnesium Salt) Tablets at the same dosage strengths)

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

j) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

k) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

l) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

Patent No.	Patent Expiration	Patent Use Code
5753675	May 19, 2015	U-998
5854259	Dec. 29, 2015	
5856336	Dec. 25, 2020	U-998
6465477	Dec. 20, 2016	
7022713	Feb. 19, 2024	U-998
8557993	Feb. 2, 2024	

No patents listed ☐ *proceed to question #14*

m) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☒ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

n) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☒ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15. (a) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement: 5856336, 6465477, 7022713, 8557993

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☒ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *7/29/15, 7/30/15 and 7/31/15*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☒ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

RICHARD E WHITEHEAD
07/14/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208379

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Zypitamag (pitavastatin magnesium) 1 mg, 2 mg and 4 mg tablets
Applicant:

Receipt Date: January 17, 2017, which constituted a complete response to our January 26, 2016, action letter

Goal Date: July 17, 2017

1. Regulatory History and Applicant's Main Proposals

This is a new drug application for Zypitamag (pitavastatin magnesium) 1 mg, 2 mg and 4 mg tablets which is being under the 505(b)(2) regulatory pathway.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

Very minor SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review. Correction will be addressed during labeling discussions with the sponsor.

1. Minor italics in cross-references in sections 4, 8, and 17

All SRPI format deficiencies of the PI identified above will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Waiver granted*

YES 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS**

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

N/A 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

NO 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment: *Some cross-reference"italics" corrected in section 4, 8, and 17*

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *Because clinical studies on pitavastatin are conducted in varying study populations and study designs, the frequency of adverse reactions observed in the clinical studies of pitavastatin cannot be directly compared with that in the clinical studies of other HMG-CoA reductase inhibitors and may not reflect the frequency of adverse reactions observed in clinical practice.*

YES 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

RICHARD E WHITEHEAD
07/11/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **July 7, 2017**

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 208379 ZYPITAMAG (pitavastatin) tablets, for oral use

On February 1, 2017 OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI) for Zypitamag. OPDP's reivew of the proposed draft PI is based on the version sent via email by Richard Whitehead on July 6, 2017. We have no comments at this time.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

ANKUR S KALOLA
07/07/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: June 22, 2017 **Date consulted:** February 2, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: The Division of Metabolic and Endocrine Products (DMEP)

Drug: Zypitamag (pitavastatin magnesium) tablets 1 mg, 2 mg and 4 mg

NDA: 208379

Applicant: Zydus Pharmaceuticals (USA) Inc.

Subject: PLLR Labeling

Indication: 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)

Materials Reviewed:

- February 2, 2017, Maternal Health, DPMH consult, DARRTS Reference ID 4050663
- January 17, 2017, Class 2 resubmission of CR, NDA 208379
- November 11, 2016, RLD labeling for NDA 22363, Livalo (pitavastatin)

- March 15, 2016, DPMH review of Crestor (rosuvastatin calcium) NDA 21366, by Christos Mastroyannis

Consult Question: "The prescribing information is required to be in the PLLR format. Please review this information."

INTRODUCTION

The Division of Metabolic and Endocrine Products (DMEP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate format and content of the pregnancy, lactation, and males and females of reproductive potential sections of pitavastatin labeling.

REGULATORY HISTORY

On January 17, 2017, Zydus Pharmaceuticals resubmitted information to NDA 208379 to address issues identified in a Complete Response Letter received on January 26, 2016 due to facility inspections. NDA 208379 is a 505(b)(2) application for pitavastatin magnesium relying on the safety and efficacy of pitavastatin calcium NDA 22363. The proposed indication is as an adjunctive therapy to diet and reduced elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B and triglycerides, and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.

BACKGROUND

Drug Characteristics[1]

Pitavastatin is an inhibitor of HMG-CoA reductase and is a synthetic lipid lower agent. Pitavastatin works by competitively inhibiting HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol. Pitavastatin has the following characteristics:

- Absolute bioavailability 51%
- Peak plasma concentrations achieved approximately 1 hour after oral administration
- C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportioned manner for single doses from 1 to 24 mg
- Distribution is more than 99% protein bound in human plasma to mainly albumin and alpha 1-acid glycoprotein
- Mean volume of distribution is 148L
- Plasma elimination half-life is 12 hours

The following serious adverse reactions were demonstrated in controlled clinical trials with pitavastatin: skeletal muscle effects, such as rhabdomyolysis with myoglobinuria, and acute renal failure and myopathy (including myositis), and liver enzyme abnormalities.

[1] November 11, 2016, RLD labeling for NDA 22363, Livalo (pitavastatin)

Hypercholesterolemia and Dyslipidemia and Pregnancy[2,3,4,5]

Normal changes occur in lipid metabolism during pregnancy in healthy females. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) levels increase throughout the pregnancy. It is believed that these elevated rises in lipid levels occur possibly due to the rise in estrogen levels which enhance lipid synthesis in the liver. Increases in TC and LDL-C have been reported in up to approximately 40% of women during pregnancy. Levels of LDL-C begin rising around the 12th week of pregnancy and peak in the second trimester. Levels of HDL-C also begin rising in the first trimester and remain high during the entire gestation. Triglyceride levels increase the most during pregnancy at approximately three-fold; however, they rapidly decline by 6 weeks post-partum.

The term 'maternal hypercholesterolemia' refers to pregnant females with cholesterol levels above that which is to be expected in an already healthy pregnancy. Both TC and TG are transferred to the placenta, metabolized and transported to the fetus. According to Vrijkotte et al. (2012),[4] high levels of TC and/or TG are associated with preterm birth, pregnancy-induced hypertension , preeclampsia and large for gestational age (LGA) infants; however, decreased levels of TC are also associated with preterm birth and increased risk of small for gestational age (SGA) infants. Additionally, the authors state that there are conflicting publications that show no association with high cholesterol levels and adverse pregnancy outcomes.

Currently statins are the drug of choice in hypercholesterolemia. However, there are conflicting reports that statins may cause teratogenicity and congenital malformation, and statins are often discontinued during pregnancy. According to the American College of Cardiology, omega-3 fatty acids can be used during pregnancy and decrease maternal TG levels. Nicotinic acid decreases TG levels while increasing HDL-C; however, there is very little evidence on the safety in pregnancy women. Fibrates are using to decrease TG, increase LDL-C and HDL-C; however, they also have very little evidence on the safety for use in pregnancy. According to Thorogood et al. (2009),[5] the National Institute of Health Clinical Excellence (NICE) guidelines recommend that women taking statins should discontinue medication three months prior to attempting to become pregnant, and women who become pregnant while taking a statin should stop treatment immediately. Additionally, the guidelines recommend that women should not start the lipid lower agent again until they have completed breastfeeding.

Current State of the Labeling of Reference Listed Drug Livalo (pitavastatin calcium)[1]

The labeling for the reference listed drug Livalo is currently in the PLR/PLLR format and was last updated in 2016. There is no boxed warning for embryofetotoxicity; however, there is a contraindication for pregnancy and lactation. The applicant submitted labeling identical to the RLD labeling. Those labeling recommendations can be found in Appendix A.

[2] Mukherjee, M, 2014, Dyslipidemia in Pregnancy, American College of Cardiology. http://www.acc.org/latest-in-cardiology/articles/2014/07/18/16/08/dyslipidemia-in-pregnancy. Accessed 9 June 2017.

[3] Avis, H et al, 2009, Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn? Curr Opin Lipidol, 20:484-490.

[4] Vrijkotte, T et al., 2012, Maternal Lipid Profile During Early Pregnancy and Pregnancy Complications and Outcomes: The ABCD Study, J Clin Endocrinol Metab, 97(11): 3917-3925.

[5] Thorogood, M et al., 2009, Management of fertility in women with familial hypercholesterolemia: summary of NICE guidance, BJOG, 116:478-479.

Pregnancy and Lactation Labeling

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[6] also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule[7] format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

PREGNANCY

Nonclinical Experience

Reproductive toxicology studies were conducted for the RLD. Pitavastatin was shown to cross the placenta in to the fetus in rats. In embryo-fetal development studies in rats treated with 3, 10 and 30 mg/kg/day during organogenesis evidence of maternal toxicity was indicated by decreased body weight gain and decreased food consumption. Neonatal malformation of agnathia (absence/partial lower jaw) was observed at the maternal no-observed-adverse-effect-level (NOAEL) of 10 mg/kg/day (82 times the human systemic exposure at 4 mg/day by area under the curve (AUC)). In pregnant rabbits treated with 0.1, 0.3 and 1 mg/kg/day during organogenesis body weight loss was seen at 6.7 times the human systemic exposure of 4 mg/day based on AUC). At maternal doses of $\geq$ 0.3 mg/kg/day spontaneous abortions and mortality were seen. The reader is referred to the full Pharmacology/Toxicology review by C. Lee Elmore, Ph.D., dated June 9, 2009 for NDA 22363 for Livalo (pitavastatin calcium).

Review of Literature

Applicant's Review of Literature[8,9,10,11,12]

The applicant provided five published articles with regard to pitavastatin and pregnancy, lactation and females and males of reproductive potential in order to support the language in those sections of labeling. Additionally, the applicant notes in the submission that the labeling in

[6] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[7] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).
[8] Cartier, J and A Goldberg, 2016, Familial Hypercholesterolemia: Advances in Recognition and Therapy, Progress in Cardiovascular Diseases, 59:125-134.
[9] Opie, L, 2015, Present status of statin therapy, Trends in Cardiovascular Medicine, 25:216-225.
[10] Jacobson, T et al., 2015, National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2, Journal of Clinical Lipidology, 9:S1-S122.
[11] Mancini, G.B et al., 2016, Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016), Canadian Journal of Cardiology, 32:S35-S65.
[12] Public Assessment Report, Pitavastatin 1 mg, 2 mg, and 4 mg film-coated tablets (pitavastatin); Kowa Pharmaceuticals Europe Company Limited.

this submission is identical to the latest approved RLD labeling. The following is the summary of published literature with regard to pregnancy as provided by the applicant:

> "Before starting a statin, women of childbearing age should receive pre-pregnancy counseling. Three months prior to conception, statins and other systemically absorbed agents should be discontinued. During pregnancy and lactation, statins should not be used and must be discontinued immediately in the event of an unplanned pregnancy. There is positive evidence of fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnancy clearly outweighs potential benefits."

DPMH's Review of Literature
DPMH conducted a search of published literature with regard to pitavastatin exposure during pregnancy using PubMed and Micromedex. Two publications were found in the PubMed search and neither was found relevant for the purposes of this review.

According to Micromedex:[13]

- *"Evidence has demonstrated fetal abnormalities or risks when [HMG-CoA reductase inhibitors] are used during pregnancy or in women of childbearing potential. An alternative to this drug should be prescribed during pregnancy or in women of childbearing potential.*
- *Pitavastatin is contraindicated in pregnancy and should be discontinued as soon as pregnancy is known. Advise women of reproductive potential to use effective contraception during pitavastatin therapy.*
- *In a prospective review of approximately 100 pregnancies in which women were 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 included in this study was adequate to only exclude a 3- to 4-fold increase in congenital anomalies over the background incidence. Notably, in 89% of these pregnancies, drug therapy was started prior to pregnancy and was discontinued during the first trimester when pregnancy was identified. Rare reports of congenital anomalies have been documented following intrauterine exposure to HMG-CoA reductase inhibitors.*
- *There are no adequate and well-controlled studies with pitavastatin in pregnant women. Pitavastatin crosses the placenta in rats and is found in fetal tissue following a single dose of 1 mg/kg/day during gestation. Teratogenicity was not evident in rats with doses of 22 times human exposure at 4 mg/kg/day based on AUC. Doses of pitavastatin greater than or equal to clinical exposure administered to pregnant rats from organogenesis through weaning contributed to maternal mortality at 3 times clinical doses and impaired lactation and decreased neonate survival in all dose groups. Reduced maternal body weight and abortion were noted in pregnant rabbits administered pitavastatin at all doses up to 4 times human exposure at 4 mg/kg/day based on AUC during fetal organogenesis.*

[13] Pitavastatin calcium. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed 9 June 2017.

- *Pitavastatin treatment in male and female rats at oral doses of 56- and 354-times, respectively, the clinical exposure at 4 mg/kg/day resulted in no adverse effects on fertility. However, mortality was observed in male and female rabbits given pitavastatin doses 30 times the clinical dose, presumably due to renal toxicity indicative of possible ischemia. While lower doses of 15 times the human exposure did not result in significant toxicity in adult rabbits, decreased implantations, increased resorptions, and decreased fetal viability were observed."*[13]

Review of Pharmacovigilance Database

The applicant submitted a cumulative review and summary of cases of pregnancy and pitavastatin use reported to their pharmacovigilance database from the time of product development to document submission. The data include four case reports listed under "pregnancy"; however, the cases involved male exposure to pitavastatin and were not related to pregnancy. The adverse events in the male patients included diarrhea, ALT increase in two of the patients and eosinophil count increase.

Summary

HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol. Based on mechanism of action, HMG-CoA reductase inhibitors, including pitavastatin, may cause fetal harm when administered to pregnant women. There are rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors; however, there are no well-controlled studies on the use of pitavastatin during pregnancy and insufficient evidence to determine a drug-associated risk of major congenital malformations or miscarriage.

Current pitavastatin labeling notes that pitavastatin is contraindicated during pregnancy. Given the lack of new published data regarding the use of pitavastatin during pregnancy and the concern for fetal harm, DPMH recommends only minor labeling edits at this time. See labeling recommendations below.

LACTATION

Nonclinical Experience

Rat studies have shown that pitavastatin is excreted into breast milk. The reader is referred to the full Pharmacology/Toxicology review by C. Lee Elmore, Ph.D., dated June 9, 2009 for NDA 22363 for Livalo (pitavastatin calcium).

Review of Literature

Applicant's Review of Literature

The applicant provided one publication with regard to pitavastatin and lactation.[11] The following is the summary of published literature with regard to lactation as provided by the applicant:

> "Data are lacking concerning levels of statins in the breast milk of mothers. However, in the absence of safety data, statins should also not be used in lactating mothers."

DPMH's Review of Literature
DPMH conducted a search of *Medication and Mother's Milk*[14], the Drugs and Lactation Database[15] (LactMed), Micromedex[13] and PubMed using the search terms "pitavastatin and lactation," "pitavastatin and breastfeeding," and no reports of clinical lactation studies or case reports were located in published literature. No results were located in the PubMed search. There was no information about pitavastatin in *Medications and Mother's Milk.*

According to Micromedex:[13]

> Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

Reviewer comment: Current labeling for HMG-CoA reductase inhibitors, including pitavastatin, contains a contraindication in breastfeeding women. Limited data on HMG-CoA reductase inhibitors, including pitavastatin, use during lactation have not indicated a specific risk to the breastfeeding infant; however, due to mechanism of action and the potential effect of HMG-CoA reductase inhibitors on cholesterol biosynthesis in a developing child, pitavastatin use is not recommended during breastfeeding. Under existing regulations 201.57(c)(5) of the Federal Food, Drug and Cosmetic Act (FD&C Act),a drug should be contraindicated only if there is a "known hazard" and not a "theoretical possibility."[16,17] DPMH recommends DMEP remove the contraindication language for HMG-CoA reductase inhibitors with regard to lactation.

Summary
There are no data on the use of pitavastatin during lactation. Pitavastatin is excreted in the milk of rats. However, due to mechanism of action and the potential effect of HMG-CoA reductase inhibitors on cholesterol biosynthesis in a developing child, pitavastatin is not recommended in breastfeeding women. Only minor edits are recommended for section 8.2, Lactation, of pitavastatin labeling. See labeling recommendations below.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience
In reproductive toxicology studies in rats, no adverse effects on male and female fertility were demonstrated at oral dose of 10 and 30 mg/kg/day respectively at exposures 56 times and 354 times the clinical exposure at 4 mg/day based on AUC. The reader is referred to the full

[14] Hale, Thomas. (2017). Medication and Mother's Milk. New York, NY. Springer Publishing Company.
[15] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[16] 201.57(c)(5) of the FD&C Act
[17] Guidance for Industry, Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products-Contents and Format. 2011. U.S. Department of Health and Human Services. Food and Drug Administration

Pharmacology/Toxicology review by C. Lee Elmore, Ph.D., dated June 9, 2009 for NDA 22363 for Livalo (pitavastatin calcium).

Review of Literature

Applicant's Review of Literature

The applicant provided one publication with regard to pitavastatin and females and males of reproductive potential.[12] The following is the summary of published literature with regard to pregnancy as provided by the applicant:

> We have not found any suspicious data which shows pitavastatin effect on human fertility. However, the preclinical safety data reflects that pitavastatin had no effect on fertility or reproductive performance and there was no evidence of teratogenic potential.

DPMH's Review of Literature

DPMH conducted a review of published literature to evaluate the use of pitavastatin and its effect on fertility, and no publication were located.

Summary

DPMH does not recommend additional changes to section 8.3, Females and Males of Reproductive Potential, at this time as there are no new human data regarding pitavastatin and infertility and no evidence of infertility in animal studies to inform a potential clinical risk. Given the concern for fetal harm, information regarding contraception will remain in section 8.3, Females and Males of Reproductive Potential.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of pitavastatin labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" section of labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" sections.
- **Lactation, Section 8.2**
  - The "Lactation" section of labeling was formatted in the PLLR format to include: the "Risk Summary," section."
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" section of labeling was formatted in the PLLR format to include the "Contraception" section to advise females of reproductive potential to use effective contraception during treatment with pitavastatin due to the potential for adverse fetal effects from maternal exposure.
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1, 8.2, and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling. (See Appendix A for the applicant's proposed pregnancy and lactation labeling)

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS----------

- Pregnancy (4, 8.1, 8.3)
- Lactation (4, 8.2)

----------USE IN SPECIFIC POPULATIONS----------

- **Females and Males of Reproductive Potential:** Advise females to use effective contraception during treatment. (8.3)

FULL PRESCRIBING INFORMATION

4 CONTRAINDICATIONS

The use of ZYPITAMAG is contraindicated in the following conditions:

- Pregnancy. *[see Use in Specific Populations (8.1, 8.3)]*.
- Lactation. It is not known if ZYPITAMAG is present in human milk; however, another drug in this class passes into breast milk. Since HMG-CoA reductase inhibitors have the potential for serious adverse reactions in breastfed infants, women who require ZYPITAMAG treatment should not breastfeed their infants *[see Use in Specific Populations (8.2)]*.

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 pitavastatin 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 are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Limited published data on pitavastatin 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 information about the presence of pitavastatin in human milk, 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. Pitavastatin is present in rat milk. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ZYPITAMAG.

8.3 Females and Males of Reproductive Potential

Contraception
Females
ZYPITAMAG may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYPITAMAG.

17 PATIENT COUNSELING INFORMATION

Embryo-fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and to inform their healthcare professional of a known or suspected pregnancy *[see Contraindications (4), Use in Specific Populations (8.1, 8.3)]*.

Lactation
Advise women not to breastfeed during treatment with ZYPITAMAG *[see Contraindications (4), Use in Specific Populations (8.2)]*.

APPENDIX A – Applicant's Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS----------

- Pregnancy (4, 8.1, 8.3)
- Lactation (4, 8.2)

----------USE IN SPECIFIC POPULATIONS----------

- **Females and Males of Reproductive Potential:** Advise females to use effective contraception during treatment. (8.3)

FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS

The use of ZYPITAMAG is contraindicated in the following conditions:

- Pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.
- Lactation. It is not known if ZYPITAMAG is present in human milk; however, another drug in this class passes into breast milk. Since HMG-CoA reductase inhibitors have the potential for serious adverse reactions in breastfed infants, women who require ZYPITAMAG treatment should not breastfeed their infants *[see Use in Specific Populations (8.2)]*.

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)]*. (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.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ZYPITAMAG may cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment with ZYPITAMAG.

17 PATIENT COUNSELING INFORMATION

Embryo-fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and to inform their healthcare professional of a known or suspected pregnancy *[see Contraindications (4), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with ZYPITAMAG *[see Contraindications (4), Use in Specific Populations (8.2)]*.

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/s/

CARRIE M CERESA
06/22/2017

MIRIAM C DINATALE
06/22/2017

LYNNE P YAO
06/27/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 28, 2017
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208379
Product Name and Strength:	Zypitamag (Pitavastatin) 1 mg, 2 mg, and 4 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Zydus Pharmaceuticals
Submission Date:	January 17, 2017 and March 6, 2017
OSE RCM #:	2015-815
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling and Prescribing Information (PI) Zypitamag (pitavastatin) NDA 208379 for areas of vulnerability that could lead to medication errors. The Division of Metabolism and Endocinology Products (DMEP) requested this review as part of their evaluation to the 505(b)(2) NDA re-submission class 2 for Zypitamag submitted on January 17, 2017.

1.1 REGULATORY HISTORY

Zydus' submission for pitavastatin under NDA 208379 is for pitavastatin magnesium. The reference listed drug (RLD) is Livalo, which was approved on August 3, 2009, under NDA 22363. The salt in Livalo is pitavastatin calcium.

Zypitamag NDA 208379 was originally submitted on March 31, 2015. The application received a Complete Response (CR) on January 26, 2016 due to facility inspections.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Zydus submitted a response to the Complete Response for Zypitamag (pitavastatin) NDA 208379. We performed a risk assessment of the container labels, carton labeling, and Prescribing Information to identify deficiencies that may lead to medication errors and other areas of improvement.

We find the proposed labels and labeling acceptable from a medication error perspective. We have no recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zypitamag that Zydus Pharmaceuticals submitted on January 17, 2017, and the listed drug (LD).

Table 2. Relevant Product Information for Zypitamag and the Listed Drug Livalo		
Product Name	**Zypitamag**	**Livalo**
Initial Approval Date	N/A	August 8th, 2009
Active Ingredient	Pitavastatin	Pitavastatin
Indication	HMG-CoA reductase inhibitor for the use of primary hyperlipidemia and mixed dyslipidemia	HMG-CoA reductase inhibitor for the use of primary hyperlipidemia and mixed dyslipidemia
Route of Administration	Oral	Oral
Dosage Form	Film Coated Tablets	Film Coated Tablets
Strength	1 mg, 2 mg, and 4 mg	1 mg, 2 mg, and 4 mg
Dose and Frequency	1 to 4 mg orally once daily at any time of the day with or without food.	1 to 4 mg orally once daily at any time of the day with or without food
How Supplied	1 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “876” on one side and plain on the other side. 2 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “877” on one side and plain on the other side. 4 mg: White to off-white, beveled-edge, round-shaped tablets debossed with “878” on one side and plain on the other side	1 mg: Round white film-coated tablet. Debossed “KC” on one side and “1” on the other side of the tablet. 2 mg: Round white film-coated tablet. Debossed “KC” on one side and “2” on the other side of the tablet. 4 mg: Round white film-coated tablet. Debossed “KC” on one side and “4” on the other side of the tablet.
Storage	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room	Store at room temperature between 15°C and 30°C (59° to 86° F) [see USP].

	Temperature]. Protect from moisture and light.	Protect from light.
Container Closure	All strengths are packaged in bottles of 30, 90, 100, 500, 1000, and unit-dose blister cartons of 100 (10 X 10) unit-dose tablets.	All strengths packaged in HDPE bottles of 90 count

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 10, 2017, we searched the L:drive and AIMS using the terms, Zypitamag, LIVALO to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous reviews and we confirmed that our recommendations were implemented or considered[1,2,3].

[1] Rahimi, L. Label and Labeling Review for Zypitamag NDA# 208379. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Oct 25. RCM No.: 2015-815

[2] Baugh, D. Label and Labeling Review for Livalo NDA# 22-363 (IND# 60,492) . Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 May 08. RCM No.: 2009-215.

[3] Baugh, D. Label and Labeling Review for Livalo NDA# 022363. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 Apr 15. RCM No.: 2010-68

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On March 13, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Ambulatory Care, and Nursing Newsletters
Search Strategy and Terms	Boolean Query: Livalo OR Pitavastatin

D.2 Results

Our results retrieved zero cases.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 13, 2017 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter[4].

Table 3: FAERS Search Strategy	
Initial FDA Receive Dates	October 01, 2015 – March 01, 2017
Product Name	Livalo
Product Active Ingredient	Pitavastatin, Pitavastatin calcium
Event (MedDRA Terms)	*Medication errors* SMQ (narrow)

E.2 Results

Our search identified 29 cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[4] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

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/s/

CASMIR I OGBONNA
04/03/2017

HINA S MEHTA
04/04/2017

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 3, 2016

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

NDA 208379 Zypitamag (pitavastatin) tablets

OPDP acknowledges receipt of your July 31, 2015, consult request regarding the proposed labeling for Zypitamag (pitavastatin) tablets. Final labeling negotiations were not initiated during this review cycle and a Complete Response letter was issued on January 26, 2016. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DMEP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these materials.

If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
02/03/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 25th, 2015
Requesting Office or Division:	Division of Metabolic and Endocrinology Products (DMEP)
Application Type and Number:	NDA 208379
Product Name and Strength:	Zypitamag (Pitavastatin) Tablets, 1 mg, 2 mg, and 4 mg
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Zydus Pharmaceuticals
Submission Date:	September 25th, 2015
OSE RCM #:	2015-815
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Yelena Maslov, Pharm.D.

1 REASON FOR REVIEW

This review is in response to a request from the Division of Metabolism and Endocrinology Products for medication error assessment of the labels and labeling for Zypitamog (pitavastatin) which the Applicant submitted as a 505 (b) (2) application.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We have reviewed the label and labeling for Zypitamag and find it acceptable from medication error perspective.

Our FAERS search and ISMP search did not identify any relevant medication error cases to this review.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation noted areas where information for the container labels and carton labeling can be improved to minimize risk for medication errors. We have made our recommendation in section 4.1 of this review.

4.1 RECOMMENDATIONS FOR THE ZYDUS PHARMACEUTICALS:

We recommend the following be implemented prior to approval of this NDA :

A. Container, Carton, and Unit-Dose Labels:

1. We recommend you provide better differentiation through additional use of color, boxing or other means among the three strengths of the product to avoid selection error. As currently presented, the only feature of differentiation among the strength is the use of differently colored boxes around the strengths (i.e. 1 mg is purple, 2 mg is (b) (4) and 4 mg is (b) (4). Although, this provides some distinction, we recommend additional means of differentiations since we have had post-marketing cases of medication errors that involved confusion between the strengths with only different colored boxes around the strength[1].

Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013 (Lines 374-375). Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zypitamag that Zydus Pharmaceuticals submitted on September 25th, 2015, and the listed drug (LD).

Table 2. Relevant Product Information for Zypitamag and the Listed Drug Livalo

Product Name	**Zypitamag**	**Livalo**
Initial Approval Date	N/A	August 8th, 2009
Active Ingredient	Pitavastatin	Pitavastatin
Indication	HMG-CoA reductase inhibitor for the use of primary hyperlipidemia and mixed dyslipidemia	HMG-CoA reductase inhibitor for the use of primary hyperlipidemia and mixed dyslipidemia
Route of Administration	Oral	Oral
Dosage Form	Film Coated Tablets	Film Coated Tablets
Strength	1 mg, 2 mg, and 4 mg	1 mg, 2 mg, and 4 mg
Dose and Frequency	1 to 4 mg orally once daily at any time of the day with or without food.	1 to 4 mg orally once daily at any time of the day with or without food
How Supplied	1 mg: White to off-white, beveled-edge, round-shaped tablets debossed with "876" on one side and plain on the other side. 2 mg: White to off-white, beveled-edge, round-shaped tablets debossed with "877" on one side and plain on the other side. 4 mg: White to off-white, beveled-edge, round-shaped tablets debossed with "878" on one side and plain on the other side	1 mg: Round white film-coated tablet. Debossed "KC" on one side and "1" on the other side of the tablet. 2 mg: Round white film-coated tablet. Debossed "KC" on one side and "2" on the other side of the tablet. 4 mg: Round white film-coated tablet. Debossed "KC" on one side and "4" on the other side of the tablet.
Storage	Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Protect from moisture and light.	Store at room temperature between 15°C and 30°C (59° to 86° F) [see USP]. Protect from light.
Container Closure	All strengths are packaged in bottles of 30, 90, 100, 500, 1000, and blister cartons of 100 (10 X 10) unit dose tablets	All strengths packaged in HDPE bottles of 90 count

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 20th, 2015, we searched the L:drive and AIMS using the terms, LIVALO to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews, and we confirmed that our recommendations were implemented or considered[2].

[2]Baugh, D. Label and Labeling Review for Livalo NDA# 22-363 (IND# 60,492) . Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 May 08. RCM No.: 2009-215.

Baugh, D. Label and Labeling Review for Livalo NDA# 022363. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2010 Apr 15. RCM No.: 2010-68

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On October 20th, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care, Ambulatory Care, and Nursing Newsletters
Search Strategy and Terms	Match Any of the Words: Livalo

D.2 Results:

Our results retrieved zero cases.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 20th, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[1]

Table 3: FAERS Search Strategy	
Date Range	**February 01, 2010- October 20th, 2015**
Product	**Livalo** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Medication Errors (HLGT) Product Label Issues (HLT)

E.2 Results

Our search identified 40 cases, but after further evaluation, we did not identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[1] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following Zypitamag labels and labeling submitted by Zydus Pharmaceuticals on September 25th, 2015.

- Container label
- Carton labeling
- Unit-Dose Blister labels
- Unit-Dose Carton Labeling
- Bulk Package Labels
- Instructions for Use

G.2 Label and Labeling Images

Container Labels: 1 mg, 2 mg, and 4 mg

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LEEZA RAHIMI
10/29/2015

YELENA L MASLOV
10/29/2015

M E M O R A N D U M

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

DATE: 8/27/2015

TO: Division of Metabolism and Endcrinology Products
Office of Drug Evaluation II

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 208379

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Requested Site(s) Inspection

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	(b) (4)
Clinical	Cliantha Research Ltd.	Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380 054 Gujarat, India

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/s/

SHILA S NKAH
08/27/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
CDER/OND/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9858

M E M O R A N D U M

DATE: June 24, 2015

FROM: Matthew Bacho, Senior RHPM
Rosemary Addy, M.H.S., SCSO
Lynne Yao, M.D., Acting Director
Division of Pediatric and Maternal Health (DPMH)

TO: Richard Whitehead, Senior RHPM
James P. Smith, M.D., M.S., Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)

NDA: 208379

DRUG: Pitavastatin Mg tablets, 1 mg, 2 mg, & 4 mg

INTRODUCTION:

On 5/13/15 DPMH received a consult from DMEP requesting assistance in drafting a Refuse-to-File (RTF) letter responding to this New Drug Application.

BACKGROUND:

The following timeline describes the actions and communications that are pertinent to this matter:

- On 5/31/13, Zydus Pharmaceuticals (USA) Inc. (Zydus) submitted Investigational New Drug Application (IND) 117674 for pitavastatin for the treatment of primary hyperlipidemia and mixed dyslipidemia;

- On 7/11/14, Zydus requested a meeting with DMEP to discuss the Agency's expectations on the pharmacology/toxicology requirements, genotoxic assessments, pediatric assessments, clinical studies, and labeling requirements for a proposed 505(b)(2) NDA. Based on this information, DMEP granted a Type C meeting;
- On 9/22/14, DMEP provided Zydus with written responses to all of its questions, including Question 13:

  Based on the information presented in the background section of Pediatric assessment, Zydus is requesting waiver for pediatric assessment study.

  FDA Response:

  > "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.
  >
  > 3.0 PREA REQUIREMENTS
  > Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.
  >
  > Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End-of-Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.
  >
  > For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm."

- On 3/31/15, Zydus submitted NDA 208379. Zydus did not include an initial pediatric study plan (iPSP), an agreed iPSP, or a pediatric assessment in this submission.

DISCUSSION:

As noted above, the applicant had been previously advised of the requirement to submit an iPSP prior to submission of their NDA. Under 505B(e), "[a]n applicant . . . shall submit to the Secretary an [iPSP] prior to submission of the assessments described in subsection (a)(2)." Under subsection (a)(1) the assessments described in (a)(2) shall be submitted "with the application." The applicant did not include an iPSP, agreed iPSP or assessment with the application. However, the applicant's intention to seek full waivers for pediatric assessments under PREA was established in the background package for the Type C meeting (see above). Furthermore, DMEP has granted full waivers for pediatric assessments under PREA for products in the same class for the same indication as this product. Finally, DMEP agrees that a full waiver for pediatric assessments under PREA would be appropriate for this product at this time. Therefore, despite the lack of an agreed iPSP submitted with this application, DPMH recommends that the lack of an agreed iPSP, in this case, should not be used as the ***sole grounds*** for a Refuse-to-File (RTF) action for this application. However, DPMH notes that if ***any*** pediatric assessments would be required under PREA for this product, the absence of an agreed iPSP would be grounds for a RTF action. Finally, for any future products in the same class for the same indication, if new clinical/scientific information is obtained that would support the need for studies in any pediatric age subset, then an agreed iPSP would be considered a required component of any marketing application and failure to include an agreed iPSP would be grounds for a RTF action.

CONCLUSION:
DPMH concludes that the lack of an agreed iPSP in this specific situation (i.e., the sponsor has clearly indicated an intent to request full waivers under PREA and the division has established a clear scientific policy that supports this approach) should not be the sole grounds for a RTF action. Therefore, DPMH recommends that the application may be filed if no other deficiencies are identified.

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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.

/s/

MATTHEW A BACHO
06/24/2015

LYNNE P YAO
06/29/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 208379

Application Type: New NDA

Name of Drug/Dosage Form: pitavastatin tablets; 1 mg, 2 mg, and 4 mg

Applicant: Zydus Pharmaceuticals (USA) Inc.

Receipt Date: March 31, 2015

Goal Date: January 31, 2016

1. Regulatory History and Applicant's Main Proposals

Zydus Pharmaceuticals (USA) Inc. (Zydus) submitted NDA 208379 on March 31, 2015. This application relies on FDA's previous findings of safety and efficacy for pitavastatin calcium (NDA 022363, Livalo) via the 505(b)(2) regulatory pathway. Zydus's product uses the magnesium salt form of pitavastatin in the same dosage form (tablets) and strengths (1 mg, 2 mg, and 4 mg) that are approved under NDA 022363.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

1. RECENT MAJOR CHANGES section should be deleted from HIGHLIGHTS.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 6, 2015. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

NO 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Note that a waiver has previously been granted for the listed product, Livalo. This comment will not be sent to the applicant as it is unlikely that their label highlights can be made to be significantly shorter than that of the listed product.*

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Name of the drug product does not appear in UPPER CASE letters.*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Selected Requirements of Prescribing Information

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

NO 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ELISABETH A HANAN
06/05/2015

RPM Filing Review Addendum

NDA 208379
Product: pitavastatin tablets (magnesium salt)
Applicant: Zydus Pharmaceuticals (USA), Inc.

My RPM Filing Review dated May 28, 2015, concluded that this application was not suitable for filing. This addendum reverses that recommendation per the Clinical Filing Review Addendum documented by Dr. James P. Smith, Deputy Director, Division of Metabolism and Endocrinology Products, on May 29, 2015.

All comments that were to be communicated to the applicant in the RTF letter per my RPM Filing Review will be communicated in the Day 74 Letter. Additional consults deferred in my RPM Filing Review will also be requested (OPDP, DMEPA, and Clinical Pharmacology study site inspections). Facility site inspections will be initiated by the Office of Pharmaceutical Quality.

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/s/

ELISABETH A HANAN
06/01/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 208379 BLA#	NDA Supplement #: S- 000 BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Animal Rule Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Pediatric
Proprietary Name: N/A Established/Proper Name: pitavastatin (magnesium salt) Dosage Form: tablets Strengths: 1 mg, 2 mg, 4 mg		
Applicant: Zydus Pharmaceuticals (USA) Inc. Agent for Applicant (if applicable): N/A		
Date of Application: March 31, 2015 Date of Receipt: March 31, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: January 31, 2016	Action Goal Date (if different): January 29, 2016	
Filing Date: May 30, 2015	Date of Filing Meeting: N/A	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☒ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Indicated as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, triglycerides and to increase HDL-C in adult patients with primary hyperlipidemia or mixed dyslipidemia.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 117674	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name***	☒	☐		

to the supporting IND(s) if not already entered into tracking system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form,*	☒	☐		

cover letter, and annotated labeling). **If yes**, answer the bulleted questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		Unexpired patents exist; applicant provided Paragraph III and Paragraph IV certification.

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it;*	☐	☒	☐	

therefore, requesting exclusivity is not required.				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	Certification was provided in narrative format, not on Form 3542a. This deficiency will be noted as a comment in the RTF letter.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		Applicant submitted Form 3454
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	☒	☐		

If yes, ensure that the application is also coded with the supporting document category, "Form 3674." ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2]	☒	☐		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☒	☐	The applicant was advised of PREA requirements in a communication issued on September 22, 2014, under IND 117674. DPMH advised that DMEP should refuse to file NDA 208379. See Memo of Filing Meeting below for further information.
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☒	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm

	☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format?[5]	☐	☐	☒	
If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☐	☒	☐	Application will not be filed
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☒	☐	Application will not be filed
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

[5] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576 htm

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	Consult request to DPMH submitted on May, 13, 2015, for documentation of their recommendation for RTF action based on lack of an Agreed iPSP.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		Applicant requested a pre-NDA meeting on July 11, 2014, under IND 117674. DMEP granted a Type C meeting for which written responses were issued on September 22, 2014.
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: N/A

BACKGROUND:

Zydus Pharmaceuticals (USA) Inc. (Zydus) submitted NDA 208379 on March 31, 2015. This application relies on FDA's previous findings of safety and efficacy for pitavastatin calcium (NDA 022363, Livalo) via the 505(b)(2) regulatory pathway. Zydus's product uses the magnesium salt form of pitavastatin in the same dosage form (tablets) and strengths (1 mg, 2 mg, and 4 mg) that are approved under NDA 022363.

Zydus submitted a pre-NDA meeting request on July 11, 2014, under IND 117674. Following review of the meeting request, the Division of Metabolism and Endocrinology Products (DMEP) determined that the request for a pre-NDA meeting was premature. DMEP instead granted a Type C Meeting with written responses and informed Zydus that they would still have an opportunity to request a pre-NDA meeting at a later date. In their meeting package, Zydus stated their intention to request a pediatric waiver for their NDA. DMEP's written responses were issued on September 22, 2014, wherein DMEP advised Zydus of the PREA requirements under FDASIA and stated that FDA would review their waiver request in the context of their complete initial Pediatric Study Plan (iPSP) submission. Zydus did not submit a subsequent pre-NDA meeting request or an iPSP as advised. Instead, Zydus submitted a Pediatric Waiver Request in their NDA. In the absence of having an Agreed iPSP in place at the time of submission for NDA 208379, the Division of Pediatric and Maternal Health (DPMH) recommended that DMEP should refuse to file the application.

Dr. Jean-Marc Guettier (Director, DMEP) and Dr. James P. Smith (Deputy Director, DMEP) concurred with the DPMH recommendation that the application should not be filed based on the lack of an Agreed iPSP and for parity across other proposed 505(b)(2) applications for the same drug class. All review disciplines have completed a filing review to identify any additional filing deficiencies and potential review issues to be communicated to the applicant. Information from these filing reviews is captured in the sections that follow. A filing meeting was not held.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Elisabeth Hanan	
	CPMS/TL:	Julie Van der Waag	
Cross-Discipline Team Leader (CDTL)	James P. Smith		
Division Director/Deputy	James P. Smith		
Office Director/Deputy	N/A		

Clinical	Reviewer:	James P. Smith	
	TL:	James P. Smith	
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Pharmacology	Reviewer:	Sze W. Lau	
	TL:	Jaya Vaidyanathan	
Biostatistics	Reviewer:	N/A	
	TL:	N/A	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Indra Antonipillai	
	TL:	Stephanie Leuenroth-Quinn	
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for protein/peptide products only)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Su Tran	
	TL:	Su Tran	
Biopharmaceutics	Reviewer	Haritha Mandula	
	TL:	Tien Mien Chen	
Quality Microbiology	Reviewer:	N/A	
	TL:	N/A	

CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	N/A	
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	N/A	
	TL:	N/A	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers/disciplines	Reviewer:	N/A	
	TL:	N/A	
Other attendees	N/A		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO The applicant completed a 28-day bridging toxicology study in rats and two bioequivalence studies comparing the proposed drug product to Livalo.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments
CLINICAL **Comments**: Review in DARRTS May 25, 2015	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: application will not be filed	☐ YES ☒ NO

• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: application will not be filed
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: Review and addendum in DARRTS dated May 11 and 26, 2015, respectively. Review issues will be communicated to the applicant in the RTF letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed? Note: The Clinical Pharmacology reviewer and the Biopharmaceutics reviewer recommend inspections for the pivotal bioequivalence study (BA1386248); however this application will not be filed.	☒ YES ☐ NO

BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: Review in DARRTS dated May 11, 2015. Review issues will be communicated to the applicant in the RTF letter.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
IMMUNOGENICITY (protein/peptide products only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**: Review in Panorama dated May 14, 2015.	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☐ YES ☒ NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> • Was the Microbiology Team consulted for validation of sterilization?	☒ Not Applicable ☐ YES ☐ NO

Comments:	
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**: Application will not be filed.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☒ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	

• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: James P. Smith, Deputy Director, DMEP

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☒	The application is unsuitable for filing. Explain why: See background summary on page 11.
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).

☐	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	351(k) BLA/supplement: If filed, send filing notification letter on day 60
☐	If priority review: • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

ELISABETH A HANAN
05/28/2015