CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208379	
Proprietary Name: Zypitamag Established/Proper Name: pitavastatin magnesium Dosage Form: 1 mg, 2 mg and 4 mg tablets	Applicant: Zydus Pharmaceuticals (USA) Inc. Agent for Applicant (if applicable):
RPM: Richard Whitehead, M.S.	Division: Division of Metabolism and Endocrinology Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)	**For ALL 505(b)(2) applications, two months prior to EVERY action:** • **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.** • **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)** ☒ No changes ☐ New patent/exclusivity *(notify CDER OND IO)* Date of check: ***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

❖ Actions	
• Proposed action • User Fee Goal Date is July 17, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	Approval 7/14/2017; Complete Response 1/26/2016
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): HMG-CoA reductase inhibitor
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Actions and dates: Approval 7/14/2017; Complete Response 1/26/2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included See final labeling in AP letter
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included See final C&C in AP letter
❖ Proprietary Name • Acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	 4/28/17; 12/15/15 4/26/17; 12/11/15
❖ Labeling reviews *(indicate dates of reviews)*	RPM-PLR format:7/11/17; 6/05/15 DMEPA: 4/04/17; 10/29/15 DMPP/PLT (DRISK): ☒ None OPDP: 7/07/17; 2/03/16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	6/01/15; 5/28/15 7/14/17
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 11/18/15 If PeRC review not necessary, explain: ____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	06/16/2017; 04/25/2017; 02/24/2017; 02/13/2017; 04/08/2016; 03/17/2016; 02/23/2016; 12/02/2015; 09/30/2015; 06/12/2015; 05/29/2015; 04/07/2015
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	Preliminary comments sent 03/15/2016; meeting request withdrawn 03/17/2016
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	none
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	7/14/2017; 01/25/2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ None see DD review
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review

• Clinical review(s) *(indicate date for each review)*	06/21/2017; 01/13/2016; 05/29/2015; 05/25/2015
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	01/13/2016 see clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	DPMH: 06/27/2017; 06/29/2015
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	12/09/2015; 05/26/2015; 05/11/2015
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	08/27/2015

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	04/24/2017; 11/24/2015; 05/11/2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	5/10/2017; 12/21/2015
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	12/21/2015
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable: 5/10/2017 Re-evaluation date: n/a

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	7/117/17
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	7/19/17

3

From: G Srinivas
To: Whitehead, Richard
Subject: RE: NDA208379 pitavastatin magnesium: Labeling
Date: Thursday, June 15, 2017 10:56:54 AM
Attachments: image001.png

Dear Dr. Rich,

This is to acknowledge receipt of your communication concerning NDA # 208379

Thanks for the update and have great rest of the day. We will follow all your directives as mentioned in your communication.

Thanks and Best Regards

Srinivas Gurram (Srini)

Vice President & Head of Regulatory Affairs
Zydus Pharmaceuticals USA Inc.
73 Route 31 North, Pennington, NJ-08534
Tel: 609-730-1900 Ext: 110
Fax:609-730-1999
e-mail: gsrinivas@zydususa.com
www.zydususa.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Thursday, June 15, 2017 9:58 AM
To: G Srinivas
Subject: NDA208379 pitavastatin magnesium: Labeling

Mr. Srinivas,

I am forwarding labeling containing FDA comments for NDA208379. Please review the comments and accept all of the tracked-change comments that you agree with. For comments that you do not agree, place a new text box stating "Applicant Comment" in tracked-change format and include your justification for concerns and return this document to FDA **within one week or receipt of this email**. Note that additional FDA comments may be coming and I will forward them if I receive any additional comments.

Let me know if you have any questions and please confirm receipt of this email.

Regards,

Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

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

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/s/

RICHARD E WHITEHEAD
06/16/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208379

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Zydus Pharmaceuticals (USA) Inc.
73 Route 31 North
Pennington, NJ 08534

ATTENTION: Srinivas Gurram
Vice President & Head of Regulatory Affairs

Dear Mr. Gurram:

Please refer to your New Drug Application (NDA) dated and received January 17, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pitavastatin Tablets, 1 mg, 2 mg and 4 mg.

We also refer to:

- Your correspondence, dated and received February 9, 2017, requesting review of your proposed proprietary name, Zypitamag
- Your amendment to the Request for Proprietary Name Review, dated and received February 14, 2017, correcting the typographical error in the proprietary name, Zypitamag.

We have completed our review of the proposed proprietary name, Zypitamag and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Richard Whitehead, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

INFORMATION REQUEST
PATENT CERTIFICATION OR VERIFICATION

Zydus Pharmaceuticals (USA), Inc.
Attention: Srinivas Gurram
Vice President and Head of Regulatory Affairs
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Gurram:

Please refer to your New Drug Application (NDA) dated and received March 31, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Pitavastatin, 1 mg, 2 mg and 4 mg tablets.

We also refer to your amendments dated January 17, March 6, and 15, 2017. This amendment does not comply with 21 CFR 314.60(f), which was added by the final rule on Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule, 81 FR 69580 (October 6, 2016). The final rule became effective on December 5, 2016.

Section 314.60(f) requires that an amendment to an unapproved 505(b)(2) application contain an appropriate patent certification or statement described in 21 CFR 314.50(i), or a "recertification" for a previously submitted paragraph IV certification, if approval is sought for changes described in any of the following types of amendments:

- To add a new indication or other condition of use;
- To add a new strength;
- To make other than minor changes in product formulation; or
- To change the physical form or crystalline structure of the active ingredient.

If an amendment to the 505(b)(2) application does not contain a patent certification (or recertification) or statement, the applicant must verify that the proposed change described in the amendment is not one of the types of amendments described above.

We recommend that the cover letter for your response to this information request and for future amendments to your unapproved 505(b)(2) application either:

1) states that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or
2) verifies that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

Your response to this information request must clearly reference your amendments dated January 17, March 6, and 15, 2017.

If you have any questions, contact me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RICHARD E WHITEHEAD
04/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

PROPRIETARY NAME ACKNOWLEDGEMENT

Zydus Pharmaceuticals (USA) Inc.
73 Route 31 North
Pennington, NJ 08534

ATTENTION: Srinivas Gurram
Vice President & Head of Regulatory Affairs

Dear Mr. Gurram:

Please refer to your New Drug Application (NDA) dated and received January 17, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pitavastatin Tablets, 1 mg, 2 mg and 4 mg.

We acknowledge receipt of your correspondence, dated and received February 9, 2017, requesting a review of your proposed proprietary name, Zypitamag.

We also acknowledge receipt of your amendment to the Request for Proprietary Name Review, dated and received February 14, 2017, correcting the typographical error in the proprietary name.

The user fee goal date is May 10, 2017.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Richard Whitehead, Regulatory Project Manager, in the Office of New Drugs at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Deveonne Hamilton-Stokes, RN, BSN, MA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DEVEONNE G HAMILTON-STOKES
02/24/2017

From: G Srinivas
To: Whitehead, Richard
Subject: RE: NDA208379 pitavastatin magnesium: Information Request
Date: Monday, February 13, 2017 9:58:28 AM

Dear Dr Richard

This is to acknowledge receipt of your communication concerning NDA 208379

Thanks for the update and have great rest of the day

Regards
Srinivas

Sent from my iPhone

-------- Original message --------
From: "Whitehead, Richard" <Richard.Whitehead@fda.hhs.gov>
Date: 2/13/17 8:16 PM (GMT+05:30)
To: G Srinivas <gsrinivas@zydususa.com>
Cc: Dhaval Desai <regulatory@zydususa.com>
Subject: NDA208379 pitavastatin magnesium: Information Request

Mr. Srinivas:

During our preliminary review of your submitted labeling for NDA 208379 for pitavastatin magnesium submitted on January 17, 2017, we found that you did not provide a review and summary of the available clinical and nonclinical information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of labeling.

Resubmit the following information by **March 6, 2017**:

- a review and summary of available nonclinical information, including published literature regarding pitavastatin use in pregnant and lactating animals and the effects of pitavastatin on male and female animal fertility (include search parameters),
- a review and summary of all available published literature regarding pitavastatin use in pregnant and lactating women and the effects of pitavastatin on male and female fertility (include search parameters),
- a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present),
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf). Use the Selected Requirements for Prescribing Information checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301 796 4945; (f) 301 796 9712; richard.whitehead@fda.hhs.gov

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/s/

RICHARD E WHITEHEAD
02/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

GENERAL ADVICE

Zydus Pharmaceuticals (USA), Inc.
Attention: G. Srinivas
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pitavastatin tablets.

We also refer to your March 30, 2016, submission, containing additional questions pertaining to FDA's Type A Meeting preliminary comments dated March 15, 2016. We also refer to your February 20, 2016, correspondence, received February 22, 2016, requesting a meeting to discuss Quality and Clinical deficiencies cited in our January 26, 2016, Complete Response letter.

We have reviewed the referenced material and have the following comments:

Zydus Question 1: *We acknowledge the Agency's response, however we seek the Agency's additional guidance on the amount of stability study data needs to be provided at the time of resubmission i.e., up to 3 months, 6 months, 12 months or 18 months?*

> **FDA's Response: You have not provided sufficient information in support of your question. In general, the amount of stability data in the resubmission will depend on which manufacturer will be included (or both manufacturers) in the resubmission and on the differences in the CMC information when comparing the manufacturers (process, equipment, controls, etc.)**

Zydus Question 2: *We acknowledge the Agency's comment however we still need additional clarification on our understanding on Safety update requirement for Zypitamag (pitavastatin magnesium) tablets. During the original NDA submission, Zydus submitted the toxicity study and comparative BE study as per the FDA recommendation.*

Considering Pitavastatin Magnesium as Molecule or Pitavastatin Tablets (magnesium salt) as drug product, neither literature nor any safety/efficacy studies has been published by any scientific institute or by any other sponsor.

As sponsor of this NDA (Zypitamag (pitavastatin magnesium) tablets), Zydus has not conducted any additional safety/efficacy studies in support of this NDA instead Zydus has relied on

Agency's finding on RLD product (Livalo® (pitavastatin) Tablet). This information was already provided in our original NDA submission.

The resubmission package in response to Complete Response Letter (CRL) would primarily consist of manufacturing of exhibit batches supported by analytical comparability study to bridge the new manufacturer to the Cadila FEI # 3002984011 supported with Bio-equivalency conducted on batches manufactured from new site as recommended by FDA.

In nutshell, the resubmission package will have similar set of data from new site as submitted in original application from FEI # 3002984011. No other additional data would be submitted for Safety Updates.

It is Zydus understanding, post approval and after commercialization of Zydus' Zypitamag (pitavastatin magnesium) tablets, a Safety update would be applicable. In addition, Zydus would submit any safety update in the resubmission if at all any literature or any safety/efficacy studies are published in public domain or performed by Zydus for Pitavastatin Magnesium as Molecule or Zypitamag (pitavastatin magnesium) tablets as drug product. We would like to have agency's concurrence on our understanding.

> **FDA Response: We agree that safety information generated from new data using pitavastatin magnesium would be part of the resubmission package. However, since you are relying on the Agency's previous determination of safety for the listed drug, Livalo, you should also submit a safety update containing any relevant new information for Livalo that becomes available before your resubmission.**

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JAMES P SMITH
04/08/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

MEETING REQUEST CANCELLED

Zydus Pharmaceuticals (USA) Inc.
Attention: G. Srinivas
Head - Regulatory Affairs
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pitavastatin tablets.

We also refer to your March 17, 2016, email communication requesting cancellation of the meeting we scheduled for March 21, 2016, because the preliminary meeting comments sent on March 15, 2016, provided additional clarification to your Quality and Clinical deficiencies cited in our January 26, 2016, Complete Response letter. The March 21, 2016, meeting has been cancelled.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RICHARD E WHITEHEAD
03/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

MEETING PRELIMINARY COMMENTS

Zydus Pharmaceuticals (USA), Inc.
Attention: G. Srinivas
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for pitavastatin tablets.

We also refer to your February 20, 2016, correspondence, received February 22, 2016, requesting a meeting to discuss Quality and Clinical deficiencies cited in our January 26, 2016, Complete Response letter.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	A
Meeting Category:	End-of-review
Meeting Date and Time:	March 21, 2016, 10-11 AM EST
Meeting Location:	telephone conference
Application Number:	NDA 208379
Product Name:	pitavastatin tablets
Indication:	Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol
Sponsor/Applicant Name:	Zydus Pharmaceuticals (USA), Inc.

FDA ATTENDEES (tentative)

Division of Metabolism and Endocrinology Products
James Smith, M.D., M.S., Deputy Director
Mary Roberts, M.D., Medical Officer
Pamela Lucarelli, Chef, Project Management Staff
Richard Whitehead, M.S., Project Manager

Office of Product Quality
Suong Tran, Ph.D., Chemist

SPONSOR ATTENDEES

Cadila Healthcare Limited, Moraiya, Ahmedabad, Gujarat, India
Vipul Doshi, President, Global Quality Assurance QA & RA
Sushrut Kulkarni, Sr. Vice President and Head Pharmaceutical Tech Center
Rajkiran Jain, Vice President- International Regulatory Affairs
Pavak Mehta, Senior General Manager - Formulation and Development

Affairs Zydus Pharmaceuticals
G. Srinivas, Head of Regulatory

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 21, 2016, 10-11AM EST, between Applicant and the Division of Metabolism and

Endocrinology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The applicant submitted a New Drug Application (NDA) for pitavastatin 1 mg, 2 mg, and 4 mg tablets on March 31, 2015. Pitavastatin is a HMG-CoA reductase inhibitor indicated for 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). This NDA is being reviewed under the 505(b)(2) regulatory pathway with Livalo (pitavastatin) tablets being the listed drug product that is the basis for the application. The application relies on clinical bioequivalence studies to establish the equivalence between this product (pitavastatin magnesium) and the innovator (pitavastatin calcium).

The application reviewed a Complete Response on January 26, 2016, because of the following Quality Facility issue: During a recent inspection of Cadila Healthcare Limited located at Sarkhej-Bavla NH No. 8A Moraiya, Taluka: Sanand, Ahmedabad, Gujurat, India, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

The purpose of this meeting is to discuss the deficiencies cited in our January 26, 2016, Complete Response letter.

2.0 DISCUSSION

2.1. Quality

Question 1: *In order to get this NDA approved if we identify another alternate cGMP compliant drug product manufacturing site besides Cadila Healthcare Limited, Moraiya (FEI #* (b) (4) *then Zydus would like to understand the activities and data that would be required to support the approval of this NDA followed by the resubmission (on complete response letter issued by the agency):*

1. *Number of drug product batches required to be executed at the proposed alternate manufacturing site,*
2. *Stability data of the drug product batch(es) required at the time of resubmission,*
3. *Bioequivalence study requirement(s).*

FDA Response to Question 1: Because the NDA has not yet been approved, information to be submitted in the resubmission in support of a new drug product manufacturer should be to the same extent that was submitted in support of the Cadila FEI# 3002984011 manufacturer if you plan to remove the Cadila FEI# 3002984011 manufacturer from the application. In addition, you need to conduct the following 2 new studies:

- A study to assess the bioequivalence under fasting between the product from the new manufacturer and the United States approved listed drug; and
- A study to assess the effect of food on the bioavailability of the product from the new manufacturer.

If both manufacturers are included in the resubmission, then an analytical comparability study can be conducted to bridge the new manufacturer to the Cadila FEI# 3002984011 manufacturer as discussed in the principles of FDA's Guidance "Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" at http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070636.pdf.

Question 2: *If the Agency concurs with Question 1 then Zydus would like to understand whether the audit of proposed alternate drug product manufacturing site shall be required for NDA approval if the site has already undergone FDA inspection and has been found acceptable within past 2 years.*

FDA Response to Question 2: We do not agree with your understanding regarding the GMP inspection of a manufacturing facility. The requirement for an inspection is determined at the time of our receipt of your resubmission and will be based on all available information in the application as well as on our internal risk and surveillance evaluations.

2.2. Clinical

Question 3: *According to 21 CFR 314.50(d)(5)(vi)(b), "The applicant shall submit these reports (1) 4 months after the initial submission; (2) in a resubmission following receipt of a complete response letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content."*

Based on the information provided above and considering the fact that no additional nonclinical/clinical studies/trials have been conducted for the drug (Pitavastatin magnesium) under consideration regardless of indication, dosage form, or dose level after NDA

submission and non-availability of other resources for worldwide experience on the safety of this drug, there is no safety updates available as of now.

Hence, Zydus is of the opinion that no safety updates will be applicable in the resubmission to the Complete Response in future. We would like to have Agency's concurrence on Zydus understanding.

> ***FDA Response to Question 3:*** If you do not believe that a safety update is applicable, provide your justification with your resubmission. In considering your justification, we will take into account the duration of time that elapses until your resubmission, as well as any accumulation of relevant scientific knowledge in the interim.

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/s/

RICHARD E WHITEHEAD
03/15/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

MEETING REQUEST GRANTED

Zydus Pharmaceuticals (USA), Inc.
Attention: G. Srinivas
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zypitamag (pitavastatin magnesium) tablets.

We also refer to your February 22, 2016, correspondence requesting a type A meeting to discuss Quality and Clinical deficiencies cited in our January 26, 2016, Complete Response letter. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The teleconference is scheduled as follows:

Date: March 21, 2016
Time: 10-11AM EST
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants:

James Smith, M.D., M.S., Deputy Director, Div. Metabolism and Endocrinology Products
Mary Roberts, M.D., Medical Officer, Div. Metabolism and Endocrinology Products
Pamela Lucarelli, Chef, Project Management, Div. Metabolism and Endocrinology Products
Richard Whitehead, M.S., Project Manager, Div. Metabolism and Endocrinology Products
Suong Tran, Ph.D., Chemist, Office of Product Quality
Anika Lalmansingh, Ph.D., Project Manager, Office of Product Quality

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

We acknowledge receipt of the meeting package included with the meeting request. **Submit 6 desk copies to me as soon as possible**. If the materials presented in the meeting package are inadequate to prepare for the meeting, we may cancel or reschedule the meeting.

Submit the **6** desk copies to the following address:

Richard Whitehead, M.S.
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3362
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Richard Whitehead, M.S.
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RICHARD E WHITEHEAD
02/23/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208379

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Zydus Pharmaceuticals (USA) Inc.
73 Route 31 North
Pennington, NJ 08534

ATTENTION: G. Srinivas
Head - Regulatory Affairs

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) dated and received March 31, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Pitavastatin Tablets, 1 mg, 2 mg, and 4 mg.

We also refer to your correspondence, dated and received September 25, 2015, requesting review of your proposed proprietary name, Zypitamag.

We have completed our review of the proposed proprietary name, Zypitamag and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 25, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Deveonne Hamilton-Stokes, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2253. For any other information regarding this application, contact Richard Whitehead, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
12/15/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

GENERAL ADVICE

Zydus Pharmaceuticals (USA) Inc.
Attention: Mr. G. Srinivas
Head - Regulatory Affairs
73 Route 31 North
Pennington, NJ 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zypitamag (pitavastatin magnesium) tablets.

We also refer to your September 25, 2015, submission, containing proposed labeling for your original NDA application.

We have reviewed the referenced material and 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].

[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

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JAMES P SMITH
12/02/2015

From: G Srinivas
To: Whitehead, Richard
Subject: RE: NDA 208379 pitavastatin: Information Request
Date: Tuesday, September 29, 2015 2:56:59 PM
Attachments: image001.png

Dear Dr. Rich,

This is to acknowledge receipt of your communication concerning NDA 208379.

Thanks for the update and we will submit response as per your directive.

Best Regards

Srinivas
Head of Regulatory Affairs
Zydus Pharmaceuticals USA Inc.
73 Route 31 North, Pennington, NJ-08534
Tel: 609-730-1900 Ext: 110
Fax:609-730-1999
e-mail: gsrinivas@zydususa.com
www.zydususa.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Tuesday, September 29, 2015 2:51 PM
To: G Srinivas
Subject: NDA 208379 pitavastatin: Information Request

Srinivas:

Please provide a response to the following request for information for NDA208379 pitavastatin tablets:

1. Provide a list of the clinical investigators involved with study BA 1386248-01 or BA 1386249-01 and whether any investigators are sponsor employees (including both full-time and part-time employees)
2. Clarify if safety or repeat labs were to be obtained under fasting conditions.

Provide this information by close-of-business, Tuesday, October 6, 2015. Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301.796.4945; (f) 301.796.9712; richard.whitehead@fda.hhs.gov

From: G Srinivas
To: Whitehead, Richard
Subject: RE: NDA208379 pitavastatin: information request
Date: Tuesday, September 29, 2015 3:00:45 PM
Attachments: image001.png

This is to confirm the receipt of your communication as enclosed below

Thanks for the update and have a great day.

Best Regards

Srinivas
Head of Regulatory Affairs
Zydus Pharmaceuticals USA Inc.
73 Route 31 North, Pennington, NJ-08534
Tel: 609-730-1900 Ext: 110
Fax:609-730-1999
e-mail: gsrinivas@zydususa.com
www.zydususa.com

From: Whitehead, Richard [mailto:Richard.Whitehead@fda.hhs.gov]
Sent: Tuesday, September 29, 2015 2:59 PM
To: G Srinivas
Subject: RE: NDA208379 pitavastatin: information request

Please also confirm receipt of this email sent earlier.

From: Whitehead, Richard
Sent: Tuesday, September 29, 2015 11:42 AM
To: 'G Srinivas'
Subject: NDA208379 pitavastatin: information request

Srinivas:

Please provide a response to the following request for information for NDA208379 pitavastatin tablets:

"Provide the location in NDA 208379 or submit the information on the composition of the high-fat breakfast in terms of caloric content for protein, carbohydrate, and fat for Study BA1386249. Refer to the food effect guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf) ."

Let me know if you have any questions and please confirm receipt of this email.

Regards,
Rich

Richard Whitehead, MS; Regulatory Project Manager; FDA/CDER/OND/ODEII/ Division of Metabolism and Endocrinology Products;
(t) 301 796 4945; (f) 301 796 9712; richard whitehead@fda hhs gov

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/s/

RICHARD E WHITEHEAD
09/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Zydus Pharmaceuticals (USA) Inc.
Attention: Mr. G. Srinivas
Head - Regulatory Affairs
73, Route 31 North
Pennington, New Jersey 08534

Dear Mr. Srinivas:

Please refer to your New Drug Application (NDA) dated March 31, 2015, received March 31, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for pitavastatin tablets; 1 mg, 2 mg, and 4 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **January 31, 2016**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team, and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by **December 31, 2015**. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Regulatory:

1. Provide patent information on form FDA 3542a as required per 21 CFR 314.53(c).

Nonclinical:

2. Provide a clean copy of the final report for study #410-1-02-8743, "4-Weeks Repeated Dose Toxicity Study of Pitavastatin Tablets 4 mg (Magnesium Salt) by Oral route in Wistar Rats with 2-Weeks Recovery Period," which is not marked (b) (4) across every page. Note the following additional comments for this study report:

    a. Separate detailed gross and histopathology summary tables are required. The histopathology tables must include the severity scores.

    b. Submit the signed statement from the reviewing pathologist on the summary of histopathology findings.

3. Provide details on qualification of all the impurities in the drug product in the pharmacology/toxicology section of your NDA, since the genetic toxicity studies have not been conducted with your formulation. Include the levels of impurities in your drug product and the levels qualified in the rat bridging toxicity study.

4. Provide details on the QSAR method used (Toxfree). In other words, submit actual data tables, drug lot numbers, purity of the tested agents, etc., so we may determine the validity of these QSAR methods (Ames TA100 by QSAR method).

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

A. 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.

B. The name of the drug product in the Highlights Limitation Statement should appear in UPPER CASE letters.

C. The Recent Major Changes section should be deleted from Highlights.

D. The Table of Contents should be in a two-column format.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **July 6, 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Metabolic and Endocrinology Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELISABETH A HANAN
06/12/2015
on behalf of Dr. Jean-Marc Guettier

From: G Srinivas
To: Hanan, Elisabeth
Subject: RE: NDA 208379 (pitavastatin)
Date: Friday, May 29, 2015 3:13:36 PM

Dear Dr. Elisabeth,

Thanks for organizing a quick call concerning subject NDA.

This is to confirm that in couple of weeks' time we will be able to provide the requested data as discussed.

Please let me know if you have any additional questions.

Thanks and have a great weekend.

Best Regards

Srinivas
Head of Regulatory Affairs
Zydus Pharmaceuticals USA Inc.
Tel: 609-730-1900 Ext:110

From: Hanan, Elisabeth [mailto:Elisabeth.Hanan@fda.hhs.gov]
Sent: Friday, May 29, 2015 2:58 PM
To: G Srinivas
Subject: NDA 208379 (pitavastatin)

Good afternoon,

Thank you for taking the time to speak to me and Dr. Smith this afternoon on short notice regarding your NDA 208379 for pitavastatin submitted on March 31, 2015. Please see below for details of the information discussed earlier via phone:

You did not submit datasets (case report tabulations) as required by 21 CFR 314.50(f)(1). The Division was not asked to agree to the deletion of tabulation datasets prior to submission of this NDA. We have determined that you must submit, at a minimum, datasets that contain the raw data for demographics, treatment allocation, exposure, laboratory data, adverse events, and vital signs. Dates of collection of safety data and dates of drug administration must be included, as well as dates (and identifying description) of all scheduled and unscheduled study visits.

In addition, you will need to submit the following information in electronic SAS transport files (.xpt) format for Studies BA1386248 and BA1386249:

a. Provide the nominal time to collect the plasma samples for the determination of pitavastatin concentrations for each participant in each study because the sampling time data for plasma pitavastatin concentrations measurements in the electronic "concentration.xpt" file are missing.

b. Provide the actual time to collect the plasma samples for the determination of pitavastatin concentrations for each participant in each study because the sampling time data for plasma pitavastatin concentrations measurements in the electronic "concentration.xpt" file are missing.

Please confirm that you will submit these datasets and provide the timeline for your submission.

Regards,

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-0350
Fax: 301-796-9712
elisabeth.hanan@fda.hhs.gov

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/s/

ELISABETH A HANAN
05/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208379

NDA ACKNOWLEDGMENT

Zydus Pharmaceuticals (USA) Inc.
Attention: Mr. G. Srinivas
Head - Regulatory Affairs
73, Route 31 North
Pennington, New Jersey 08534

Dear Mr. Srinivas:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: pitavastatin tablets; 1 mg, 2 mg, and 4 mg

Date of Application: March 31, 2015

Date of Receipt: March 31, 2015

Our Reference Number: NDA 208379

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **May 30, 2015**, in accordance with 21 CFR 314.101(a).

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-0350.

Sincerely,

{See appended electronic signature page}

Elisabeth A. Hanan, M.S.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELISABETH A HANAN
04/07/2015