CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation:
Approval
(including the Overall Manufacturing Inspection Recommendation)

NDA 208379
Review #2
Review Date (see last page)

Drug Name/Dosage Form	Pitavastatin Tablets
Strength	1 mg, 2 mg and 4 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Zydus Pharmaceuticals
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	3/31/2015
0006	10/01/2015
0013	1/17/2017

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/Office
Application Team Lead	Suong (Su) Tran	New Drug Products II/ONDP
Regulatory Business Process Manager	Anika Lalmansingh	Regulatory Business Process Management I/OPRO
Drug Substance	Erika Englund	New Drug API/ONDP
Drug Product	Elise Luong	New Drug Products II/ONDP
Biopharmaceutics	Haritha Mandula	Biopharmaceutics/ONDP
Process	Yong Wang	Process Assessment II/OPF
Microbiology	Yong Wang	Process Assessment II/OPF
Facility	Marisa Stock Heayn Allison Aldridge Vidya Pai	Inspectional Assessment/OPF

Executive Summary

I. Recommendation

The recommendation from the Office of Pharmaceutical Quality (OPQ) is for Approval, including the Overall Manufacturing Inspection Recommendation dated 5/8/2017.

II. Summary

This current recommendation for Approval replaces the 12/21/2015 recommendation for a Complete Response due to a "Withhold" Overall Manufacturing Inspection Recommendation for the drug product manufacturer Cadila Healthcare Limited located at Sarkhej-Bavla NH No. 8A Moraiya, Taluka: Sanand, Ahmedabad, Gujurat, India. As per the attached Facilities review, the most recent inspection of this manufacturer (completed on 2/16/2017) resulted in a No Action Indicated classification, which led to the current OPQ recommendation for Approval.

OVERALL ASSESSMENT AND SIGNATURE: EXECUTIVE SUMMARY

Application Technical Lead Signature:

Suong T. Tran -S

Digitally signed by Suong T Tran -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suong T Tran -S, 0.9.2342.19200300.100.1.1=1300101829
Date: 2017.05.10 09:36:56 -04'00'

Suong (Su) Tran, Ph.D.

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Comparability Protocols

Reviewer's Assessment: N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

N/A

List of Deficiencies: None

Primary Facilities Reviewer Name and Date: Allison A. Aldridge, Ph.D., 5/3/2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Vidya Pai, OPF/DIA/B3, 04 May 2017

Allison Aldridge

Digitally signed by Allison Aldridge
Date: 5/08/2017 11:29:04AM
GUID: 508da7170002981da764ca33dfb39a19

Vidya Pai

Digitally signed by Vidya Pai
Date: 5/05/2017 10:25:15AM
GUID: 53b581d20000464509a65e37ec9ad4a2

Su (Suong) Tran

Digitally signed by Su (Suong) Tran
Date: 5/10/2017 09:38:31AM
GUID: 508da71f00029ec8b75e233f12b15339

Recommendation:
Complete Response

NDA 208379
Review #1
Review Date (see page 7)

Drug Name/Dosage Form	Pitavastatin Tablets
Strength	1 mg, 2 mg and 4 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Zydus Pharmaceuticals
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
0000	3/31/2015
0006	10/01/2015

Quality Review Team

DISCIPLINE	REVIEWER	DIVISION/Office
Application Team Lead	Suong (Su) Tran	New Drug Products I/ONDP
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Table of Contents

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	Adequate	19-NOV-2015	by E. Englund/D. Christner
	III			Adequate	08-DEC-2015	by E. Luong/D.. Christodoulou Per MAPP "CMC Reviews of Type III DMFs for Packaging Materials" the referenced Type III DMFs need not be reviewed for solid dosage forms.
	III					
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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22363	RLD: Livalo

2. CONSULTS: n/a

Executive Summary

I. Recommendation:

The recommendation from the Office of Pharmaceutical Quality (including the manufacturing inspection recommendation) is for a **Complete Response** (see issues below).

Labeling comments will be finalized during the multi-disciplinary review managed by OND.

A. Recommendation and Conclusion on Approvability

1. **Summary of Complete Response issues**: Cadila Healthcare Limited located at Sarkhej-Bavla NH No. 8A Moraiya, Taluka: Sanand, Ahmedabad, Gujurat, India, is the proposed drug product manufacturer. This site was most recently inspected in September 2014 as a site-wide surveillance coverage. Numerous cGMP deficiencies related to the manufacture of solid oral dosage form products were identified. A 483 was issued (b) (4)
2. **Action letter language**: "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."
3. **Benefit/Risk Considerations**: The benefit/risk ratio is minimal because 1) patients have another FDA-approved product (Livalo) currently available in the U.S. with the same active ingredient (different salt), and 2) the new product, subject of this review, would not not be marketed as a generic option, thus negating any potential monetary savings for patients.

B. Recommendation on Post-Approval Commitments, Agreements, and/or Risk Management Steps: not applicable

II. Summary of Quality Review

A. Drug Substance:

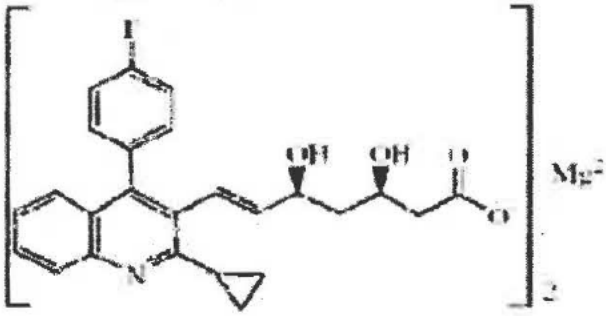
DMF (b) (4) is referenced for all CMC information on Pitavastatin Magnesium. The DMF was found adequate to support this NDA on 19-NOV-2015 by ONDP/DNDAPI (E. Englund/D. Christner).

APPEARS THIS WAY ON ORIGINAL

USAN: pitavastatin

HMG-CoA reductase inhibitor

INN:	Pitavastatin
Compendial name:	Not Applicable
Chemical Name:	(3R,5S)-7-[2-Cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl]3,5-dihydroxy-6(E)-heptanoic acid hemi magnesium
CAS:	[956116-90-8]



Pitavastatin Magnesium

$C_{50}H_{46}MgF_2N_2O_8$; MW = 865.23

The applicant provides a comparison of the physical properties of pitavastatin calcium and pitavastatin magnesium in the NDA. The primary difference between the salts is solubility, the magnesium salt being more soluble in aqueous media. The drug substance has the BCS designation of "highly soluble". It is a hygroscopic white to off white powder that is freely soluble in acetone and ethyl acetate; soluble in dimethylsulfoxide, and insoluble in dichloromethane and isopropyl alcohol. It has an optical rotation of 21- 24 °, a pH of 7.3, a pKa of 5.31 and melts at 207 °C. The drug substance is (b) (4) .

Information on the drug substance manufacture (including starting materials, synthetis, process, container closure, and retest period of (b) (4) is submitted in DMF (b) (4) (currently adequate).

The regulatory drug substance specification in the NDA is consistent with the drug substance specification in DMF (b) (4) both found adequate for this type of active ingredient based on the supporting release and stability data. The only impurity with a limit higher than the applicable ICH qualification threshold is (b) (4) at (b) (4)%, which was considered acceptable by the Application Team Lead and the Pharmacology Toxicology team. One impurity, (b) (4), has a structural alert for genotoxic potential. However, it was found genotoxic-negative using Quantitative Structure-Activity Relationship by the CDER Computational Toxicology

Consultation Service and thus qualified per ICH M7, and it is controlled as a non-genotoxic impurity/degradant per current ICH Q3A.

B. Drug Product

Each film-coated tablet contains pitavastatin magnesium equivalent to 1 mg, 2mg, and 4 mg pitavastatin:
1 mg are white to off-white, beveled-edge, round shaped tablets debossed with "876" on one side and plain on the other side;
2 mg are white to off-white, beveled-edge, round shaped tablets debossed with "877" on one side and plain on the other side;
4 mg are white to off-white, beveled-edge, round shaped tablets debossed with "878" on one side and plain on the other side.

Excipients are calcium carbonate, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, and sodium carbonate anhydrous. The film-coating contains hypromellose, polyethylene glycol, talc and titanium dioxide. [redacted] (b) (4) NDA includes an acceptable BSE/TSE risk statement for the compliance with EMEA/410/01rev2.

The manufacturing process consists of [redacted] (b) (4)

The regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. One impurity, [redacted] (b) (4) from the drug substance discussion, is also a product degradant. Consistent with the drug substance review, this compound is controlled as a non-genotoxic degradant per current ICH Q3B.

Container Closure systems:
30-, 90-, 100-, 500-, or 1000- count HDPE bottles and 10- count blister packs

Expiration Date & Storage Conditions: 24 months at room temperature, protected from moisture and light.

C. Summary of Drug Product Intended Use

Proprietary Name of the drug product	[not yet finalized by GRMP goal. See the CDTL's review]
Non-proprietry name of the drug product	pitavastatin tablet

Established Name	pitavastatin
Proposed Indication(s)	[not yet finalized by GRMP goal. See the CDTL's review]
Duration of Treatment	chronic
Maximum Daily Dose	4 mg
Alternative Methods of Administration	not applicable

D. Biopharmaceutics Considerations:

One single-dose fasting bioequivalence study and one single-dose food-effect study were conducted to compare the 4 mg strength of the new product to the reference listed product Livalo 4 mg (details of these studies are found in the Clinical Pharmacology review).
The comparative dissolution profiles of the 1 mg and 2 mg strengths of the new product are comparable to that of the higher strength 4 mg used in the in-vivo BE study. Similarity factor (f2) values were not calculated because more than (b)(4)% of the drug release was observed in (b)(4) minutes. Based on the data, a biowaiver is granted for the 1 mg and 2 mg strengths of the new product from a Biopharmaceutics perspective under 21 CFR 320.22 (d) (2).

E. Novel Approaches: not applicable

F. Any Special Product Quality Labeling Recommendations: not applicable

G. Life Cycle Knowledge Information (see Attachment)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Team Lead Signature:

Suong T. Tran -S

Su (Suong) Tran, PhD