

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200153Orig1s000

CHEMISTRY REVIEW(S)

Final Addendum to CMC Reviews

From: Su (Suong) Tran, CMC Lead, ONDQA
To: NDA 200153 (ezetimibe/atorvastatin)
Subject: Final ONDQA recommendation for NDA 200153

This addendum is on behalf of the Compliance/OMPQ:

The EES overall recommendation dated 02-MAY-2013 is ACCEPTABLE.

Conclusion: The final ONDQA recommendation for NDA 200153 is APPROVAL with no pending issue and including the overall recommendation “Acceptable” from Compliance/OMPQ.

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

/s/

SUONG T TRAN
05/03/2013

NDA 200153

**ATOZET™
(Ezetimibe/Atorvastatin)
Oral Tablet**

**MSD International GmbH
(formerly MSP Singapore Company, LLC)**

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #2

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations.....	7
A. Recommendation and Conclusion on Approvability.....	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	11
A. Reviewer's Signature: in DAARTS	11
B. Endorsement Block: in DAARTS	11
C. CC Block: in DAARTS.....	11
Chemistry Assessment	12

Chemistry Review Data Sheet

1. NDA 200153
2. REVIEW #: 2
3. REVIEW DATE: 06-Dec-2011
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Original NDA

Document Date

29-Apr-2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

NDA Amendment

Document Date

22-Sept-2011

7. NAME & ADDRESS OF APPLICANT:

Name: MSD International GmbH

Address: Weyrstrasse 20, 6000 Lucerne 6, Switzerland

Representative: Catherine Kohler, Pharm D, Agent for MSD International GmbH

Telephone: 267-305-3510

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ATOZET™

b) Non-Proprietary Name (USAN): Ezetimibe/Atorvastatin

c) Code Name/# (ONDC only): MK-0653C

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New Combination)
- Submission Priority: Standard

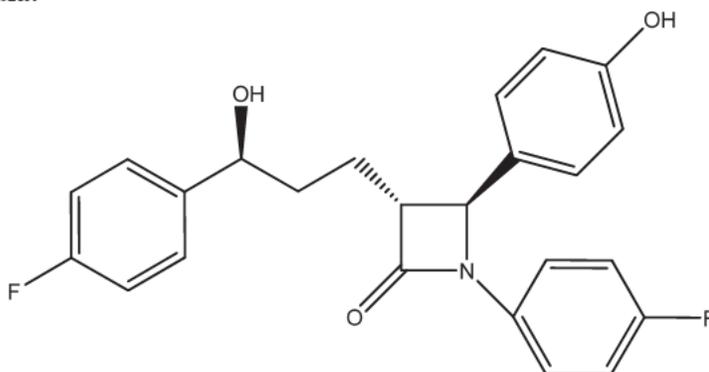
Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY: The ezetimibe/atorvastatin tablet contains ezetimibe, an anticholesteremic agent and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, as therapy for patients with hypercholesterolemia.
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY:
ATOZET™ tablets are manufactured in four strengths (ezetimibe/atorvastatin): 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg. Atorvastatin is calculated as the free acid.
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Ezetimibe

Chemical Name: 1-(4-Fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone

Structural Formula:



Chemistry Review Data Sheet

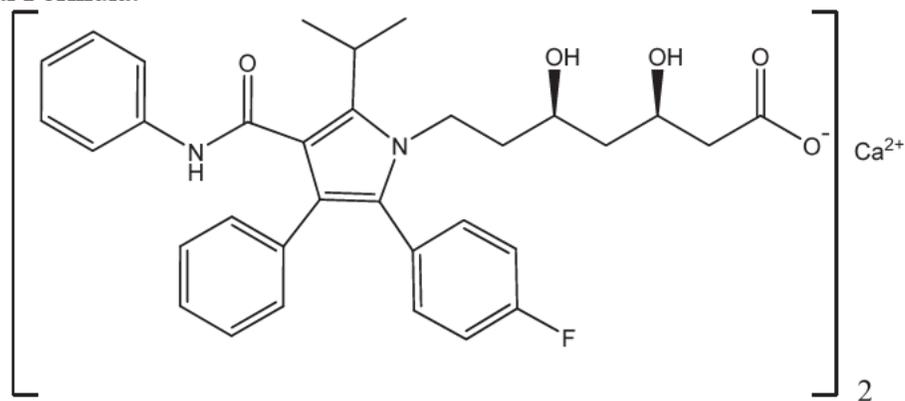
Molecular Formula: C₂₄H₂₁F₂NO₃

Molecular Weight: 409.4

B. Atorvastatin

Chemical Name: [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1)

Structural Formula:

Molecular Formula: C₆₆H₆₈CaF₂N₄O₁₀

Molecular Weight: 1155.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	10-Jun-2008	Reviewed by J. Hill
	IV			1	Adequate	18-Apr-2011	Reviewed by L. Qi
	III			1	Adequate	15-Dec-2010	Reviewed by E. Jao
	III			1	Adequate	22-Nov-2010	Reviewed by P. Jiang
	III			1	Adequate	12-Mar-2009	Reviewed by B. Kurtyka
	III			1	Adequate	9-Feb-2009	Reviewed by K. Raman

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	1	Adequate	19-Jul-2010	Reviewed by C. Bertha
	III		1	Adequate	03-Jun-2011	Reviewed by J. Leginus
	III		1	Adequate	18-Jun-2008	Reviewed by R. Agarwal

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-445	ZETIA® (Ezetimibe)
NDA	20-702	LIPITOR® (Atorvastatin Calcium)
IND	101,953	Ezetimibe/Atorvastatin Combination

18. STATUS:
ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	An Overall Compliance recommendation of Acceptable has been provided.	04-Dec-2011	N/A
Biopharm	Recommended for Approval.	28-Oct-2011	Deepika Lakhani
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	N/A
EA	Categorical Exclusion Requested under 21 CFR §25.31(b).	N/A	N/A
Microbiology	Not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth.	N/A	N/A
QbD	N/A		

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 200153

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 200153 is recommended for Approval from the standpoint of chemistry, manufacturing and controls.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

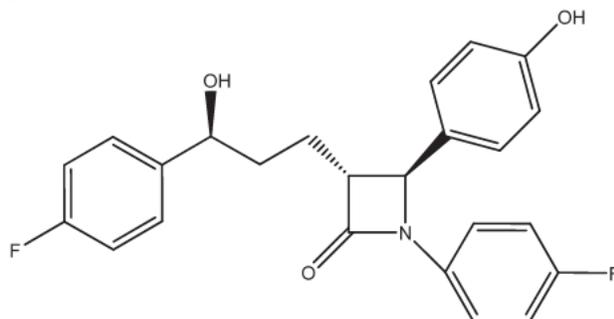
II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCES

Ezetimibe

Ezetimibe, approved in 2002 (NDA 21-445, ZETIA®), is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. It is a white, crystalline powder that is freely to very soluble in ethanol, methanol and acetone and practically insoluble in water. The empirical formula of ezetimibe is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4. The structural formula of ezetimibe is:

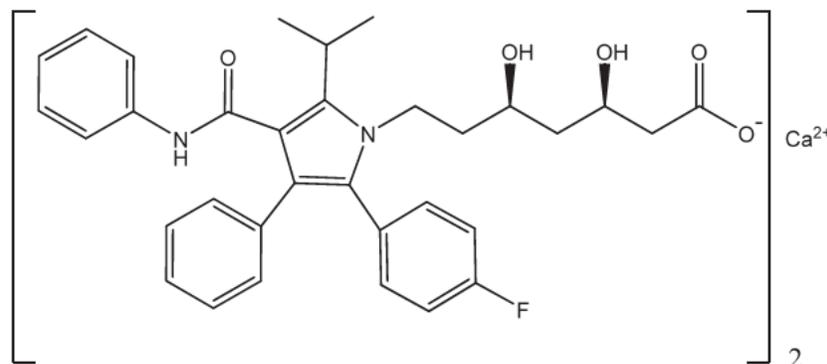


Information for ezetimibe is provided in the sponsor's approved NDA 21-445 and is incorporated by reference herein.

Executive Summary Section

Atorvastatin Calcium (amorphous)

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis. It is a white to off-white amorphous powder that is very slightly soluble in water, practically insoluble in acetonitrile and freely soluble in methanol. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.37. The structural formula of atorvastatin calcium is:



Information for atorvastatin calcium (amorphous) has been provided in Dr. Reddy's Type II DMF 18468 and is incorporated by reference herein. DMF 18468 was reviewed on 10-Jun-2008 and found to be adequate. A copy of the letter of authorization to reference DMF 18468 has been provided.

DRUG PRODUCT

ATOZET™ is formulated as a fixed dose combination, immediate-release, film-coated (b) (4) tablet for oral administration containing two drug substances, ezetimibe and atorvastatin calcium (amorphous). Four dosage strengths containing a fixed dose of ezetimibe (10 mg) and a variable dose of atorvastatin (10, 20, 40 or 80 mg calculated as the free acid) have been developed and are represented as follows:

Ezetimibe/Atorvastatin 10 mg/10 mg
Ezetimibe/Atorvastatin 10 mg/20 mg
Ezetimibe/Atorvastatin 10 mg/40 mg
Ezetimibe/Atorvastatin 10 mg/80 mg

Product development focused on manufacturing a chemically and physically stable combination tablet that was bioequivalent to the co-administered ezetimibe (ZETIA®) and atorvastatin (LIPITOR®) monotherapy tablets.

Four Ezetimibe/Atorvastatin tablet strengths (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg) are manufactured (b) (4)

Executive Summary Section

(b) (4)

Excipients used in the manufacture of Ezetimibe/Atorvastatin Tablets (lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, lactose anhydrous, hydroxypropyl cellulose, and sodium bicarbonate) are of compendial grade with the exception of the film coat, (b) (4). However, (b) (4) is manufactured using the compendial ingredients (hydroxypropyl cellulose, hypromellose (b) (4) and titanium dioxide).

The proposed release specifications include ezetimibe and atorvastatin identity (HPLC and UV), assay (HPLC), degradates (HPLC), content uniformity and dissolution; appearance and moisture (Karl Fischer). All non-compendial regulatory methods have been validated.

The drug product will be packaged in tablet (b) (4) in a vented (b) (4) blister with push-through aluminum lidding. The (b) (4)/aluminum blister card is enclosed in a (b) (4) plastic case (for child-resistance) which is contained in a (b) (4) aluminum pouch along with two (b) (4) oxygen scavenger canisters and one (b) (4) desiccant. Venting of the blister card allows any oxygen or moisture associated with the tablet to be sequestered by the oxygen scavenger and desiccant contained in the foil pouch. This packaging format reduces degradation of the oxygen-, moisture- and light-sensitive atorvastatin component of the drug product. Ezetimibe is not moisture-, oxygen- or light-sensitive.

The applicant has provided 24 months of acceptable real time stability (25°C/60% RH) data for three batches for each of the 10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg strengths in the primary packaging. A bracketing strategy was used with regard to the intermediate strength (10 mg/40 mg strength) and therefore, it was not placed into the stability program. Additional acceptable stability data was generated at an accelerated condition (40°C/75% RH) through six months. Based on these data, a shelf-life of 24 months is granted for all strengths of Ezetimibe/Atorvastatin Tablets when stored in the primary packaging at the recommended storage condition of 20° - 25°C/60% RH, which is consistent with the applicant's proposed shelf life of the drug product.

B. Description of How the Drug Product is Intended to be Used

ATOZET™ has been developed as an immediate release (b) (4) tablet containing a fixed-dose of ezetimibe combined with variable doses of atorvastatin. The combination tablet contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. ATOZET is proposed as therapy for patients with

Executive Summary Section

primary hypercholesterolemia, including heterozygous familial hypercholesterolemia. The goal of the ezetimibe/atorvastatin combination product was to establish comparable safety and efficacy between the combination tablet and the corresponding individual ezetimibe and atorvastatin tablets when co-administered. The ezetimibe/atorvastatin tablet formulation is intended to provide a more convenient single tablet when a combination of the two drugs is prescribed.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has satisfactorily addressed all items in the List of Deficiencies from Chemistry Review #1 in their 22-Sept-2011 amendment to the original NDA. See Chemistry Assessment section below for details.

Acceptable cGMP recommendations have been received from the Office of Compliance for all manufacturing and testing facilities. An Overall Compliance recommendation of Acceptable was provided on 04-Dec-2011.

A recommendation for approval was received from the biopharmaceutics product quality standpoint (10/28/2011).

The applicant filed the NDA as a 505(b)(2) application providing for a new combination oral tablet. The reference listed drug (RLD) is Lipitor® (atorvastatin calcium) from a different applicant (Pfizer). It should be noted that the RLD is crystalline atorvastatin whereas the atorvastatin in the new combination product is amorphous. Reference is made to the applicant's approved NDA 21-445 for all CMC information on the ezetimibe drug substance. Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance.

This NDA was initially refused by FDA for filing on 10/29/2009 for several CMC deficiencies. The NDA was resubmitted on 4/29/2011 and includes responses to each filing deficiency and other nonfiling comments detailed in the 10/29/2009 letter. The associated IND is 101,953 which was received on 5/16/2008.

Drug substance ezetimibe will be manufactured for commercial use by MSD International GmbH (Singapore Branch) referenced to the applicant's NDA 21-445. Drug substance atorvastatin calcium (amorphous) will be manufactured for commercial use by Dr. Reddy's Laboratories located in India with CMC information provided in the Type II DMF No. 18468. A copy of the letter of authorization to reference DMF 18468 has been provided. The DMF was reviewed and found to be adequate.

The drug product, ATOZET™ (ezetimibe/atorvastatin) Tablet, will be manufactured by MSD International GmbH located in Puerto Rico as an immediate-release film-coated combination product comprised of ezetimibe and atorvastatin (b)(4) containing the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, lactose

Executive Summary Section

anhydrous, hydroxypropyl cellulose, and sodium bicarbonate). All excipients are of compendial grade with the exception of the film coat, (b) (4) however, (b) (4) is manufactured using the following compendial ingredients: hydroxypropyl cellulose, hypromellose (b) (4) and titanium dioxide.

The atorvastatin portion of ATOZET was found to be oxygen-, moisture- and photosensitive. The primary packaging (vented (b) (4)/aluminum blister card enclosed in a (b) (4) aluminum pouch along with two oxygen scavenger canisters and one (b) (4) desiccant) provides adequate protection during shelf life.

Based on the supporting real time and accelerated stability data, a shelf life of 24 months at the recommended storage condition of 20° - 25°C/60% RH is granted for ATOZET.

(b) (4)

III. Administrative

- A. Reviewer's Signature: in DAARTS
- B. Endorsement Block: in DAARTS
- C. CC Block: in DAARTS

13 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

JOSEPH M LEGINUS
12/06/2011

ALI H AL HAKIM
12/06/2011

NDA 200153

**ATOZET™
(Ezetimibe/Atorvastatin)
Oral Tablet**

MSP Singapore Company, LLC

**Joseph Leginus, PhD
Division of Pre-Marketing Assessment III, Branch VII, ONDQA**

**For the Division of
Metabolism and Endocrinology Products**

CHEMISTRY REVIEW #1

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	12
A. Reviewer's Signature: in DAARTS	12
B. Endorsement Block: in DAARTS	12
C. CC Block: in DAARTS.....	12
Chemistry Assessment	13
I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data	13
S DRUG SUBSTANCE.....	13
P DRUG PRODUCT	21
A APPENDICES	73
R REGIONAL INFORMATION	73
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	76
A. Labeling & Package Insert.....	76
B. Environmental Assessment or Claim of Categorical Exclusion	87
List of Deficiencies To Be Communicated	88

Chemistry Review Data Sheet

1. NDA 200153
2. REVIEW #: 1
3. REVIEW DATE: 23-Aug-2011
4. REVIEWER: Joseph Leginus, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA

Document Date

29-Apr-2011

7. NAME & ADDRESS OF APPLICANT:

Name: MSP Singapore Company, LLC

Address: 300 Beach Road #12-08, The Concourse, Singapore 199555

Representative: Jeffrey R. Tucker, M.D., Senior Director, Regulatory Affairs, Merck.

Telephone: 267-305-6715

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ATOZET™

b) Non-Proprietary Name (USAN): Ezetimibe/Atorvastatin

c) Code Name/# (ONDC only): MK-0653C

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4 (New Combination)
- Submission Priority: Standard

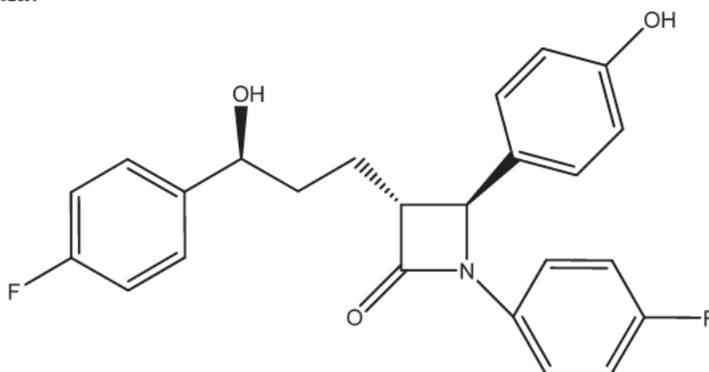
Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: This NDA is submitted as a 505(b)(2) application.
10. PHARMACOL. CATEGORY: The ezetimibe/atorvastatin tablet contains ezetimibe, an anticholesteremic agent and atorvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, as therapy for patients with hypercholesterolemia.
11. DOSAGE FORM: Tablet
12. STRENGTH/POTENCY:
ATOZET tablets are manufactured in four strengths (ezetimibe/atorvastatin): 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg. Atorvastatin is calculated as the free acid.
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):
 SPOTS product – Form Completed
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

A. Ezetimibe

Chemical Name: 1-(4-Fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone

Structural Formula:



Chemistry Review Data Sheet

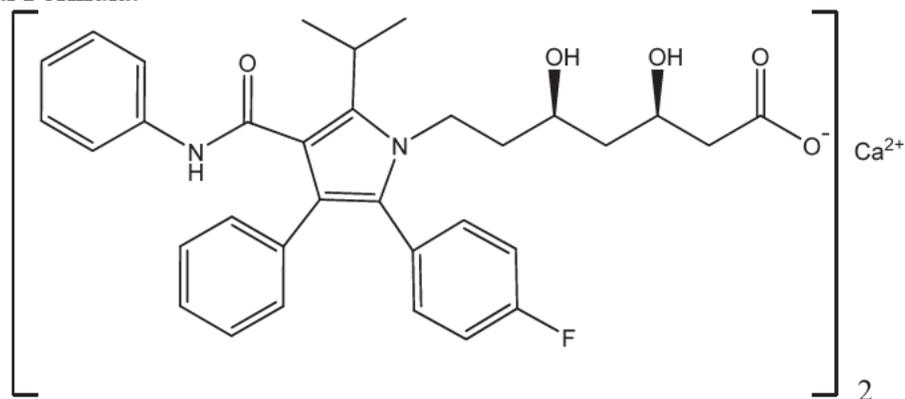
Molecular Formula: C₂₄H₂₁F₂NO₃

Molecular Weight: 409.4

B. Atorvastatin

Chemical Name: [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1)

Structural Formula:

Molecular Formula: C₆₆H₆₈CaF₂N₄O₁₀

Molecular Weight: 1155.37

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	10-Jun-2008	Reviewed by J. Hill
	IV			1	Adequate	18-Apr-2011	Reviewed by L. Qi
	III			1	Adequate	15-Dec-2010	Reviewed by E. Jao
	III			1	Adequate	22-Nov-2010	Reviewed by P. Jiang
	III			1	Adequate	12-Mar-2009	Reviewed by B. Kurtyka
	III			1	Adequate	9-Feb-2009	Reviewed by K. Raman

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	1	Adequate	19-Jul-2010	Reviewed by C. Bertha
	III		1	Adequate	03-Jun-2011	Reviewed by J. Leginus
	III		1	Adequate	18-Jun-2008	Reviewed by R. Agarwal

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-445	ZETIA® (Ezetimibe)
NDA	20-702	LIPITOR® (Atorvastatin Calcium)
IND	101,953	Ezetimibe/Atorvastatin Combination

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending. All facilities are Acceptable except the drug product manufacturer (Merck, Arcibo, PR). Inspection assigned to Investigations Branch.	03-Jun-2011	N/A
Biopharm	A request for the Biopharmaceutics evaluation of dissolution data was made.	23-May-2011	Deepika Lakhani
Methods Validation	Validation may be requested of FDA labs after test methods are finalized.	N/A	N/A
EA	Categorical Exclusion Requested under 21 CFR §25.31(b).	N/A	N/A

Chemistry Review Data Sheet

Microbiology	Not required as per ICH Q6A. The solid dosage form has been shown during development not to support microbial viability or growth.	N/A	N/A
--------------	--	-----	-----

19. ORDER OF REVIEW: N/A

The Chemistry Review for NDA 200153

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The recommendation from the standpoint of chemistry, manufacturing and controls is pending a satisfactory response to the deficiencies delineated in the List of Deficiencies and Information Request (in CMC Review #1 for NDA 200153).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

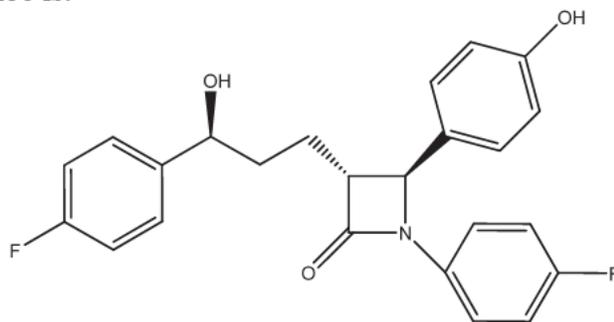
II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCES

Ezetimibe

Ezetimibe, approved in 2002 (NDA 21-445, ZETIA®), is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. It is a white, crystalline powder that is freely to very soluble in ethanol, methanol and acetone and practically insoluble in water. The empirical formula of ezetimibe is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.4. The structural formula of ezetimibe is:

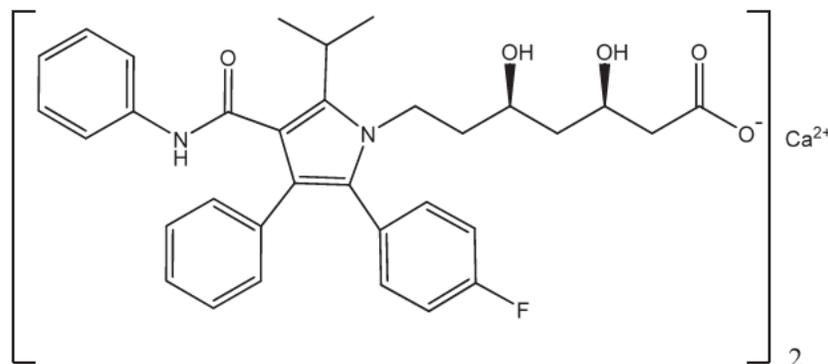


Information for ezetimibe is provided in the sponsor's approved NDA 21-445 and is incorporated by reference herein.

Executive Summary Section

Atorvastatin Calcium (amorphous)

Atorvastatin calcium is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol biosynthesis. It is a white to off-white amorphous powder that is very slightly soluble in water, practically insoluble in acetonitrile and freely soluble in methanol. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.37. The structural formula of atorvastatin calcium is:



Information for atorvastatin calcium (amorphous) has been provided in Dr. Reddy's Type II DMF 18468 and is incorporated by reference herein. DMF 18468 was reviewed on 10-Jun-2008 and found to be adequate. A copy of the letter of authorization to reference DMF 18468 has been provided.

DRUG PRODUCT

ATOZET™ is formulated as a fixed dose combination, immediate-release, film-coated (b) (4) tablet for oral administration containing two drug substances, ezetimibe and atorvastatin calcium (amorphous). Four dosage strengths containing a fixed dose of ezetimibe (10 mg) and a variable dose of atorvastatin (10, 20, 40 or 80 mg calculated as the free acid) have been developed and are represented as follows:

Ezetimibe/Atorvastatin 10 mg/10 mg
Ezetimibe/Atorvastatin 10 mg/20 mg
Ezetimibe/Atorvastatin 10 mg/40 mg
Ezetimibe/Atorvastatin 10 mg/80 mg

Product development focused on manufacturing a chemically and physically stable combination tablet that was bioequivalent to the co-administered ezetimibe (ZETIA®) and atorvastatin (LIPITOR®) monotherapy tablets.

Four Ezetimibe/Atorvastatin tablet strengths (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg and 10 mg/80 mg) are manufactured (b) (4)

Executive Summary Section

(b) (4)

Excipients used in the manufacture of Ezetimibe/Atorvastatin Tablets (lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, lactose anhydrous, hydroxypropyl cellulose, and sodium bicarbonate) are of compendial grade with the exception of the film coat, (b) (4). However, (b) (4) is manufactured using the compendial ingredients (hydroxypropyl cellulose, hypromellose (b) (4) and titanium dioxide).

The proposed release specifications include ezetimibe and atorvastatin identity (HPLC and UV), assay (HPLC), degradates (HPLC), content uniformity and dissolution; appearance and moisture (Karl Fischer). All non-compendial regulatory methods have been validated.

The drug product will be packaged in tablet (b) (4) in a vented (b) (4) blister with push-through aluminum lidding. The (b) (4)/aluminum blister card is enclosed in a (b) (4) plastic case (for child-resistance) which is contained in a (b) (4) aluminum pouch along with two (b) (4) oxygen scavenger canisters and one (b) (4) desiccant. Venting of the blister card allows any oxygen or moisture associated with the tablet to be sequestered by the oxygen scavenger and desiccant contained in the foil pouch. This packaging format reduces degradation of the oxygen-, moisture- and light-sensitive atorvastatin component of the drug product. Ezetimibe is not moisture-, oxygen- or light-sensitive.

The applicant has provided 24 months of acceptable real time stability (25°C/60% RH) data for three batches for each of the 10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg strengths in the primary packaging. A bracketing strategy was used with regard to the intermediate strength (10 mg/40 mg strength) and therefore, it was not placed into the stability program. Additional acceptable stability data was generated at an accelerated condition (40°C/75% RH) through six months. Based on these data, a shelf-life of 24 months is granted for all strengths of Ezetimibe/Atorvastatin Tablets when stored in the primary packaging at the recommended storage condition of 20° - 25°C/60% RH, which is consistent with the applicant's proposed shelf life of the drug product.

B. Description of How the Drug Product is Intended to be Used

ATOZET™ has been developed as an immediate release (b) (4) tablet containing a fixed-dose of ezetimibe combined with variable doses of atorvastatin. The combination tablet contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and atorvastatin, a 3-hydroxy-3- methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. ATOZET is proposed as therapy for patients with

Executive Summary Section

primary hypercholesterolemia, including heterozygous familial hypercholesterolemia. The goal of the ezetimibe/atorvastatin combination product was to establish comparable safety and efficacy between the combination tablet and the corresponding individual ezetimibe and atorvastatin tablets when co-administered. The ezetimibe/atorvastatin tablet formulation is intended to provide a more convenient single tablet when a combination of the two drugs is prescribed.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation from a CMC perspective is pending satisfactory responses to the deficiencies identified in Review #1.

This is a 505(b)(2) application providing for a new combination oral tablet. The reference listed drug (RLD) is Lipitor (atorvastatin calcium) from a different applicant (Pfizer). It should be noted that the RLD is crystalline atorvastatin whereas the atorvastatin in the new combination product is amorphous. Reference is made to the applicant's approved NDA 21-445 for all CMC information on the ezetimibe drug substance. Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance.

This NDA was initially refused by FDA for filing on 10/29/2009 for several CMC deficiencies. The NDA was resubmitted on 4/29/2011 and includes responses to each filing deficiency and other nonfiling comments detailed in the 10/29/2009 letter. The associated IND is 101,953 which was received on 5/16/2008.

Drug substance ezetimibe will be manufactured for commercial use by MSD International GmbH (Singapore Branch) referenced to the applicant's NDA 21-445. Drug substance atorvastatin calcium (amorphous) will be manufactured for commercial use by Dr. Reddy's Laboratories located in India with CMC information provided in the Type II DMF No. 18468. A copy of the letter of authorization to reference DMF 18468 has been provided. The DMF was reviewed and found to be adequate.

The drug product, ATOZET® (ezetimibe/atorvastatin) Tablet, will be manufactured by MSD International GmbH located in Puerto Rico as an immediate-release film-coated combination product comprised of ezetimibe and atorvastatin (b)(4) containing the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, lactose anhydrous, hydroxypropyl cellulose, and sodium bicarbonate). All excipients are of compendial grade with the exception of the film coat, (b)(4) however, (b)(4) is manufactured using the following compendial ingredients: hydroxypropyl cellulose, hypromellose (b)(4) and titanium dioxide.

The atorvastatin portion of ATOZET was found to be oxygen-, moisture- and photosensitive. The primary packaging (vented (b)(4)/aluminum blister card enclosed in a

Executive Summary Section

(b) (4) aluminum pouch along with two oxygen scavenger canisters and one (b) (4) desiccant) provides adequate protection during shelf life.

Based on the supporting real time and accelerated stability data, a shelf life of 24 months at the recommended storage condition of 20° - 25°C/60% RH is granted for ATOZET.

(b) (4)

III. Administrative

- A. Reviewer's Signature: in DAARTS
- B. Endorsement Block: in DAARTS
- C. CC Block: in DAARTS

76 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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

/s/

JOSEPH M LEGINUS
08/23/2011

ALI H AL HAKIM
08/23/2011

Initial Quality/CMC Assessment
ONDQA

Division of Metabolism and Endocrinology Products

NDA: 200153

Applicant: MSP Singapore Co., LLC

Stamp Date: 29-APR-2011

PDUFA Date: 29-FEB-2012

Proposed Proprietary Name: Atozet

Established Name: Ezetimibe/atorvastatin calcium

Dosage form and strength: Immediate release tablet –
10/10, 10/20, 10/40, and 10/80 mg/mg
ezetimibe/atorvastatin (free acid)

Route of Administration: oral

Indications: Treatment of hypercholesterolemia

CMC Lead: Su (Suong) Tran, ONDQA

ONDQA Fileability: Yes

Initial Quality/CMC Assessment
ONDQA

CONSULTS/ CMC RELATED REVIEWS	COMMENT
EA	The categorical exclusion claim will be assessed by Primary Reviewer.
Compliance (DMPQ)	EER was sent to Compliance by ONDQA PM (K. Sharma) on 12-MAY-2011.
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
ONDQA Biopharm	Review of all dissolution/drug release-related information and any biowaiver issue. (Reviewer: Deepika Lakhani)
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>

This is an electronic NDA, filed as a 505(b)(2) application, with the listed drug (LD) being Lipitor (atorvastatin calcium) from a different applicant (Pfizer). It should be noted that the LD is crystalline atorvastatin and this new combination product has amorphous atorvastatin.

Reference is made to the approved NDA 21445 (same applicant: MSP Singapore) for all CMC information on the ezetimibe drug substance.

Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance.

The product is a fixed dose combination, immediate-release (b) (4) tablet available in the strengths of 10/10, 10/20, 10/40, and 10/80 mg/mg ezetimibe/atorvastatin (free acid). In support of efficacy, pivotal bioequivalence (BE) studies, P145 and P183, were conducted to compare the combination tablet to the concomitantly administered individual approved Zetia (ezetimibe) and Lipitor (atorvastatin) for all 4 combination dosage strengths 10/10, 10/20, 10/40, and 10/80 mg/mg ezetimibe/atorvastatin (free acid).

Maximum daily dose is 10/80 mg/mg ezetimibe/atorvastatin (free acid).

Initial Quality/CMC Assessment
ONDQA

Has all information requested during the IND phases and at the pre-NDA meeting been included?
Yes.

Reviewer's comment: This NDA was initially refused by FDA for filing on 29-OCT-2009 for several CMC deficiencies. This resubmitted NDA includes a response to each filing deficiency and other non-filing comments.

FDA's 29-OCT-2009 filing deficiencies and the applicant's responses (The responses allow for the filing of the NDA. The reviewer will evaluate the responses as part of the NDA review.):

1. You indicate that the manufacturing and testing facilities are currently not ready for GMP inspections. Therefore, this NDA is considered to be incomplete and cannot be filed until all facilities involved in the manufacturing and testing of the commercial product are ready for GMP inspections.

Response: All facilities involved in the manufacturing and testing of commercial product are ready for GMP inspections.

2. Provide the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54.

Response: The unexecuted master production records are provided in Sec. 3.2.R.4.

3. Your primary stability batches were manufactured at an R&D facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data as well as multipoint dissolution profiles.)

Response: Three months of long term and accelerated stability data have been generated on batches manufactured at the commercial manufacturing site and are provided in Sec. 3.2.P.8.3.1 and Sec. 3.2.P.8.3.2, respectively. Data are presented from three batches of each strength that were placed on stability for the primary stability study (10 mg/10 mg, 10 mg/20 mg and 10 mg/80 mg). These data include multipoint dissolution profiles.

Initial Quality/CMC Assessment ONDQA

The following filing deficiency was from ClinPharm, who was the discipline responsible for dissolution data that the time of the first NDA submission. For the current submission, the ONDQA Biopharm team will evaluate the dissolution information.

FDA Filing Deficiency 4: The application did not include any information to bridge the performance of the clinically tested batches to the commercial products (e.g. multipoint *in vitro* dissolution profiles).

Response: Multipoint dissolution profiles generated on the bioequivalence batches of each strength have been compared with batches manufactured at the commercial site and the data are provided in Sec. 3.2.P.8.1.6.7. In addition, the 10 mg/10 mg, 10 mg/20 mg, and 10 mg/80 mg bioequivalence batches were also part of the primary stability study. The dissolution data for ezetimibe and atorvastatin show similar release profiles between the bioequivalence batches and commercial product. The four bioequivalence batches (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg) were the only clinically tested batches of the fixed dose combination product.

The following issues were not filing deficiencies but were included in the 29-OCT-2009 letter. The responses allow for the filing of the NDA. The reviewer will evaluate the responses as part of the NDA review.

1. We remind you that, regarding the reference to CMC information in NDA 21445 Zetia, only the approved information can be referenced.

Response: The Sponsor understands that only approved CMC information can be referenced from NDA 21-445 (ZETIA®).

2. Provide samples of the container closure system, including the vented blister, plastic case, and foil pouch.

Response: Physical samples of the container closure system for the trade package will be provided at the time this application is submitted to the Agency. These samples include the vented blister, plastic case and foil pouch as well as the oxygen scavengers and desiccant. The container closure system is described in Sec. 3.2.P.7.

Initial Quality/CMC Assessment
ONDQA

(b) (4)

3. Clarify whether the materials of construction are the same for all packaging systems (commercial, hospital use, and sample) and indicate the tablet counts in the sample packaging.

Response: The materials of construction are the same for all packaging systems (commercial, hospital use and sample). As child resistance is not required for the hospital or sample packages, the ^{(b) (4)} plastic case is not utilized in those package systems. The tablet counts for the trade package, sample package, and Hospital Unit Dose (HUD) are ten, seven, and one, respectively.

4. A complete NDA should be submitted with at least 12-month primary stability data at the long term storage condition. Your NDA is submitted with 26 weeks of stability data at the long term storage condition of 25 °C/60% RH and at the accelerated condition of 40 °C/75% RH. While we may attempt to review unsolicited amendments submitted during the review cycle, the review of such amendments will depend on the timeliness of the submission, extent of the submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and

Initial Quality/CMC Assessment ONDQA

Practices (GRMPPs) timelines, we cannot guarantee that we will review unsolicited amendments such as your proposed stability update.

Response: The primary stability batches contain at least 18-month stability data (24-month data for eight of the nine primary stability batches) at the long term condition of 25°C/60% RH and six months at the accelerated condition of 40°C/75% RH as reported in Sec. 3.2.P.8.3 and Sec. 3.2.P.8.4, respectively.

5. Your primary stability batches and clinical batches used in the pivotal bioequivalence studies were manufactured at an R&D facility. Provide multipoint dissolution profiles comparing these batches and the to-be-marketed product.

Response: Multipoint dissolution profiles comparing stability/bioequivalence batches and to-be marketed product (i.e. batches manufactured at the commercial site) are provided in Sec. 3.2.P.8.1.6.7. The dissolution data for ezetimibe and atorvastatin show similar release profiles between the stability/bioequivalence batches and to-be marketed product.

6. In addition to the comparative impurity results submitted in your 05-OCT-2009 communication, provide physicochemical data as requested by FDA on 30-JUN-2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. This information is required in support of the 505(b)(2) application.

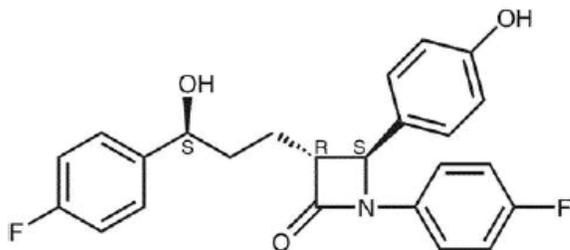
Response: Comparative impurity results as well as physicochemical data are provided in Sec. 3.3.R.3.

Initial Quality/CMC Assessment ONDQA

Drug substance:

Ezetimibe

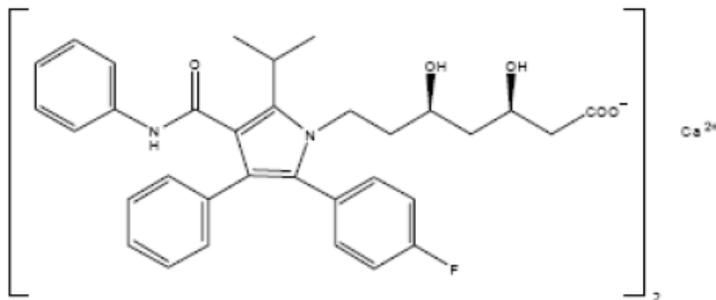
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature [Ref. 5.4: 4290].

Atorvastatin

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1).. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.36. Its structural formula is:



Atorvastatin calcium is a white to off-white powder that is very slightly soluble in water, insoluble in acetonitrile, and soluble in methanol [Sec. 3.2].

Review comments:

Reference is made to the approved NDA 21445 for all CMC information on the ezetimibe drug substance. Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance. No specific comment regarding atorvastatin calcium (amorphous) can be discussed in this review because the CMC information is in a DMF. The primary reviewer will review any information in the DMF that has not been evaluated. Because different polymorphs of atorvastatin may have different solubilities (BCS Class II) and in vivo profiles, the reviewer will evaluate the adequacy of the proposed X-ray powder diffraction test and acceptance criteria used to assure consistent polymorphic quality of this drug substance.

Specifications are copied on pages 21-24.

Initial Quality/CMC Assessment
ONDQA

Drug product

The composition of the drug product is copied below.

Ezetimibe/Atorvastatin FDC Tablet – Market Composition

Components	Compendial Testing	Function	Unit Strength (Ezetimibe/Atorvastatin)			
			10/10 mg/mg	10/20 mg/mg	10/40 mg/mg	10/80 mg/mg
(b) (4)						
Ezetimibe (SCH58235)	---	Active	mg/tablet 10.00			
(b) (4)						
Atorvastatin Calcium ⁵ (amorphous) (equivalent free acid) [¶]	---	Active	10.34 (10.00)	20.68 (20.00)	41.36 (40.00)	82.73 (80.00)
(b) (4)						
Film-Coating:	(b) (4)					
Total Coated Tablet Wt :			624.0 mg	364.1 mg	519.7 mg	830.3 mg
(b) (4)						

- **Proportionality of dosage strengths.** (b) (4)

Initial Quality/CMC Assessment
ONDQA

(b) (4)

- **Established name and dosage strength.** The proposed established names of the product are “ezetimibe” and “atorvastatin”, which are acceptable because they correlate with the dosage strength as per current CDER policy on nomenclature. The drug substances are ezetimibe and atorvastatin calcium. The dosage strength for atorvastatin is based on the free acid.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the formulation (called “Final Market Image”, or FMI) is the same for the pivotal BE batches, primary stability batches, and commercial product. The BE and stability batches were manufactured at 1/10th the scale of the commercial manufacture and at the R&D site in West Point PA. As requested by FDA, dissolution data and stability data are submitted to bridge the West Point site to the commercial manufacturing site in Arecibo PR to the R&D site via “site stability” or “site demonstration” batches WL00039711 (10/10), WL00039712 (10/20), WL00039713 (10/40), and WL00039714 (10/80). The dissolution data will be reviewed by the ONDQA Biopharm team as part of the biowaiver request evaluation.

Manufacturing process of the drug product

(b) (4)

Review comments:

- **Atorvastatin degradation.** The drug substance is oxygen-, light-, and moisture-sensitive. The reviewer will document information on the controls used during manufacture to minimize the degradation of the material.
- **Expiry dating.** The dating period of the drug product starts (b) (4)
(b) (4)
(b) (4)
(b) (4)
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the pivotal BE batches and primary stability batches were manufactured at 1/10th the scale of the commercial manufacture and at the R&D site in West Point PA. As requested by FDA, dissolution data and stability data are submitted to bridge the commercial manufacturing site in Arecibo PR to the R&D site. The applicant states that the commercial process is similar to that used for the pivotal BE batches and primary stability batches with the following differences: (b) (4)
(b) (4)
(b) (4)
- **Master batch records.** These records are not included in the NDA for the commercial manufacturing process (to comply with 505(b)(2) regulations)

Batch information:

Initial Quality/CMC Assessment
ONDQA

For the 10/10 strength

Film-Coated Tablets

Batch number	WL00031196 [¶]	WL00031690	WL00031691	WL00039711 [†] (Arecibo Lot 0000055077)
Use	Stability	Biobatch/Stability	Stability	Site Stability
Drug Substance Batches Ezetimibe	080300800	080200484	080200485	100100160 (b) (4)
Atorvastatin Calcium (b) (4)	ABBH003996	ABBH004055 (b) (4)	ABBH003996/ ABBH004055	ABDH004037/ ABDH004127 (b) (4)
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA	Arecibo, PR (b) (4)
Theoretical batch size (tablets)				
Manufacturing date	Sep 2008	Sep 2008	Sep 2008	Oct 2010

For the 10/20 strength

Film-Coated Tablets

Batch number	WL00031197	WL00031693	WL00032969	WL00039712 [†] (Arecibo Lot 0000045411)
Use	Biobatch/ Stability	Stability	Stability	Site Stability
Drug Substance Batches Ezetimibe	080300800	080200485	080200484	100100160 (b) (4)
Atorvastatin Calcium (b) (4)	ABBH003996 (b) (4)	ABBH003996/ ABBH004055 (b) (4)	ABBH005576 (b) (4)	ABCH006413/ ABCH006415/ ABCH006416 (b) (4)
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA	Arecibo, PR (b) (4)
Theoretical batch size (tablets)				
Manufacturing date	Sep 2008	Sep 2008	Feb 2009	Jul 2010

Initial Quality/CMC Assessment
ONDQA

For the 10/40 strength

Batch number	WL00034555	WL00039713 (Arecibo Lot 0000045029)
Use	Biobatch	Site Demonstration
Drug Substance Batches Ezetimibe	080300800	100100160 (b) (4)
Atorvastatin Calcium (b) (4)	ABBH005576 (b) (4)	ABCH006413/ ABCH006415/ ABCH006416 (b) (4)
Drug Product Manufacturing Site	West Point, PA	Arecibo, PR (b) (4)
Theoretical batch size (tablets)		
Manufacturing date	May 2009	Jul 2010

For the 10/80 strength

Batch number	WL00031198	WL00031694	WL00031695	WL00039714 ¹ (Arecibo Lot 0000045206)
Use	Biobatch/Stabil ity	Stability	Stability	Site Stability
Drug Substance Batches Ezetimibe	080300800	080200484	080200485	100100160 (b) (4)
Atorvastatin Calcium (b) (4)	ABBH003996	ABBH004055 (b) (4)	ABBH003996/ ABBH004055 (b) (4)	ABCH006413/ ABCH006415/ ABCH006416 (b) (4)
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA	Arecibo, PR (b) (4)
Theoretical batch size (tablets)				
Manufacturing date	Sep 2008	Sep 2008	Sep 2008	Jul 2010

Initial Quality/CMC Assessment
ONDQA

Drug product specification

The proposed drug product specification is copied on pages 25-26 of this review.

Review comments:

- **Dissolution.** Review of all dissolution/drug release-related information will be conducted by the ONDQA Biopharm team.
- **Moisture content.** The water activity is less than (b) (4) and the moisture content in the drug product specification is limited to (b) (4) both being thresholds for potential microbial growth. The moisture limit is also important because atorvastatin is moisture-sensitive.
- **Limits on degradation products.** The applicant states that there is no impurity difference between the new product and the approved products.
 - The only degradant related to ezetimibe is (b) (4) with a limit of (b) (4) which is below the ICH identification threshold for the maximum daily dose of 10 mg.
 - The atorvastatin-related degradants are copied in the table below.

The limits on (b) (4) ((b) (4) for 10 mg and (b) (4) for the higher dosage strengths), (b) (4) and (b) (4) are less than the ICH qualification threshold of 0.5% for a maximum daily dose of 80 mg atorvastatin.

The limits on (b) (4) are (b) (4) for the 10 mg atorvastatin and (b) (4) for the higher dosage strengths, which are qualified as per ICH guidelines for an impurity that is also an inactive metabolite of the drug substance.

A limit is proposed on the sum of (b) (4) and (b) (4) because these impurities interconvert in the presence of water in the test method diluent, with the dominant one being (b) (4). The limit of the sum is (b) (4) which is less than the ICH qualification threshold of 0.5% for each impurity.

Initial Quality/CMC Assessment
ONDQA

Atorvastatin Impurities

A1906M02/A1906M08 (Atorvastatin Assay by HPLC)	Impurity Name	Primary Mechanism
(b) (4)		

(b) (4)

Initial Quality/CMC Assessment ONDQA

Container closure systems for product distribution

The drug product will be packaged in a vented (b) (4) blister with push-through aluminum lidding. The (b) (4) aluminum blister card is enclosed in a (b) (4) plastic case (for child-resistance) which is contained in a (b) (4) aluminum pouch along with two oxygen scavengers and one (b) (4) desiccant (b) (4). The aluminum pouch is composed of (b) (4).

Venting of the blister card allows for the free exchange of oxygen and moisture between the tablet contained in the blister cavity and the oxygen scavenger and desiccant contained in the foil pouch. The oxygen scavengers and desiccant contained in the aluminum pouch provide the proper environment for the product over the proposed shelf-life.

A range of tablet counts, (b) (4) is supported for the trade and sample packages. The current sample package contains a tablet count of seven. The current trade package contains a tablet count of ten. A single-tablet Hospital Unit Dose (HUD) package is also supported. As child-resistance is not required for this hospital package or for sample packages, the (b) (4) case is not utilized in those cases. The materials of construction for all packages including the sample, trade, and HUD are the same.

Protection, Safety, Compatibility and Performance information for the container closure system is provided in Sec 3.2.P.7-0653c-tablet.

Review comments:

- **Protective properties of the complete packaging system.** The applicant proposes to include oxygen scavengers and a desiccant in the secondary packaging system (foil pouch) as well as a vented primary packaging system (blister) to address the oxygen- and moisture- sensitive nature of atorvastatin. The reviewer will confirm that the complete packaging system can adequately protect the product through its shelf life, and that adequate instructions are included in the labeling for the storage of the product in the intact (i.e., sealed) foil pouch. Once the patient opens the foil pouch, an in-use shelf life of 30 days is proposed (see the Stability discussion later in this review.)
- **Information on the primary packaging components.** The applicant identifies the product-contact surfaces to be the (b) (4) blister film and the aluminum lidding foil (b) (4). References to the CFR for their components are provided, which will be confirmed by the reviewer.

Initial Quality/CMC Assessment ONDQA



Stability of the drug product

8.1.1 Stability Summary and Conclusions

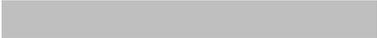
The stability of Ezetimibe/Atorvastatin FDC Tablet is presented as a compilation of data generated from the Formal Stability Studies (FSS), which have been conducted in accordance with ICH Guidelines. Up to 104 weeks of formal stability data are included in this application.

The Formal Stability Studies indicate satisfactory stability of the product in package for 104 weeks at the long term storage condition of 25°C/60%RH and for 26 weeks at the accelerated condition of 40°C/75%RH. No significant changes were observed at any storage condition.

Based on the data presented, the proposed stability updates and the corresponding evaluations, the applicant proposes an initial shelf life of 24 months for Ezetimibe/Atorvastatin FDC Tablet when stored at 20-25°C (68-77°F).

The product package provides protection from light, moisture, and oxygen. Therefore, it is recommended to store tablets in the original foil pouch until use. After the foil pouch is opened, protect from moisture and light, store in a dry place and discard unused tablets after 30 days.

Review comments:

- Three batches of each of the 10/10, 10/20, and 10/80 mg/mg ezetimibe/atorvastatin were designated primary stability batches. The 10/40 strength was bracketed  (b) (4)  and will be packaged in the same container closure systems. One stability batch of each strength was also a biobatch in the pivotal BE studies. Photostability data are included in the package.

Initial Quality/CMC Assessment ONDQA

- As previously requested by FDA, stability data of the drug product from the commercial sites are submitted to bridge to the primary stability batches from the R&D manufacturing site: one batch of each of the 10/10, 10/20, and 10/80 strengths, with three months of accelerated data and multipoint dissolution profiles.
- The packaging system consists of oxygen scavengers and a desiccant in the secondary packaging system (foil pouch) as well as a vented primary packaging system (blister) to address the oxygen- and moisture- sensitive nature of atorvastatin. As discussed earlier in this review, the reviewer will confirm that the complete packaging system can adequately protect the product through its shelf life, and that adequate instructions are included in the labeling for the storage of the product in the intact (i.e., sealed) foil pouch. Once the patient opens the foil pouch, an in-use shelf life of 30 days is proposed, and the applicant includes data in support of this in-use period. The reviewer will evaluate the data and confirm that adequate instructions are included in the labeling for this in-use shelf life.

Supporting NDA or IND:

IND 101953: same sponsor

NDA 21445 Zetia (ezetimibe): same applicant

Supporting DMF:

DMF's Referenced in the NDA

<u>DMF No.</u>	<u>Supplier</u>	<u>Purpose</u>
(b) (4)		

Initial Quality/CMC Assessment
ONDQA

GMP facilities:

ESTABLISHMENT INFORMATION:

Manufacturing Sites Listed in the NDA

Drug Substance - Ezetimibe
<u>Manufacturing, Packaging, Release and Stability Testing:</u> MSD International GmbH (Singapore Branch) 50 Tuas West Drive Singapore 638408 Establishment Registration No. 3002808083 Contact: Dr. Gaetan Angoh General Manager Phone: 65-68698752 Fax: 65-68698759

Drug Substance – Atorvastatin
<u>Manufacturing, Packaging, Release and Stability Testing:</u> Dr. Reddy's Laboratories Limited Chemical Technical Operations – Unit-II Plot No. 110 & 111 Sri Venkateswara Co-operative Industrial Estate Bollaram, Jinnaram Medak District Andhra Pradesh India Establishment Registration Number: 3005448030 Contact: Maria Wirths Executive Director External Manufacturing Quality Assurance Phone: 215-652-3540 Fax: 215-993-0663

Initial Quality/CMC Assessment
ONDQA

Drug Product
<u>Manufacturing:</u> Ezetimibe (b) (4) Schering Plough (Singapore) Pte Ltd 70 Tuas West Drive Singapore 638414 Establishment Registration No. 3004199021 Contact: Dr. Gaetan Angoh General Manager Phone: 65-68698752 Fax: 65-68698759
<u>Manufacturing:</u> Atorvastatin (b) (4) Patheon Pharmaceuticals Inc. 2110 E. Galbraith Rd. Cincinnati, OH 45237-1625 U.S.A Establishment Registration No. 1510437 Contact: Maria Wirths Executive Director External Manufacturing Quality Assurance Phone: 215-652-3540 Fax: 215-993-0663
<u>Manufacturing:</u> (b) (4) MSD International GmbH (Puerto Rico Branch) LLC Road #2, Kilometer 60.3 Sabana Hoyos Arecibo PR 00688 Establishment Registration No. 2650235 Contact: Licette Lopez Quality Operations Director Phone: 787-623-7356 Fax: 787-623-7119
<u>Packaging</u> Anderson Packaging Inc. 4545 Assembly Drive Rockford IL 61109 Establishment Registration No. 1421377 Contact: Maria Wirths Executive Director External Manufacturing Quality Assurance Phone: 215-652-3540 Fax: 215-993-0663

Initial Quality/CMC Assessment
ONDQA

Packaging, Stability Testing

Merck Sharp & Dohme Corp.
4633 Merck Road
Wilson, North Carolina 27893
USA
Establishment Registration No. 1036761

Contact: Pam Mills
Quality Operations Director
Phone: 252-246-6379
Fax: 252-246-6209

Sites Used During Development

Drug Product

Process and Analytical Development, Manufacturing, Release Testing, and Stability Monitoring and Testing

Merck Sharp & Dohme Corp.[†]
770 Sumneytown Pike
West Point, PA 19486-0004, USA
Establishment Registration No. 2510592

[†]Responsible for the Merck dedicated laboratory at Pharmaceutical Manufacturing Research Services, Inc. (PMRS) and any contract facilities used during development.

Contact: Stephen Yu
Research & Development/Commercialization Quality Site Head
Phone: 908-473-7530
Fax: 908-473-3783

Initial Quality/CMC Assessment
ONDQA

DRUG SUBSTANCE SPECIFICATION

Ezetimibe Specification	
Test	Acceptance Criteria
Description [†]	White powder
Identification	(b) (4)
Infrared Spectrum [†] (SCH 58235)	
Chiral HPLC (b) (4)	
Moisture (KF) [†]	
Specific Rotation ([α]D ₂₀ , 10 mg/mL in methanol)	
Heavy Metals	
Sulfated Ash	
Assay (Achiral HPLC) [†]	
Related Compounds	
Achiral Related Compounds [†]	
(b) (4)	

Initial Quality/CMC Assessment
ONDQA

Test	Acceptance Criteria
(b) (4)	(b) (4)
Particle Size† Release Shelf Life	(b) (4)
† These tests are required for recertification testing.	

Initial Quality/CMC Assessment
ONDQA

Atorvastatin Calcium (amorphous) Specification

Test	Specification	Analytical Procedure
Description	White to off-white powder	Visual
Identification IR-Spectrum Test for calcium Water by KF Heavy Metals Related Substances by HPLC ²	(b) (4)	
(b) (4)		
Assay by HPLC		

Initial Quality/CMC Assessment
ONDQA

Test	Specification	Analytical Procedure
(b) (4)		(b) (4)
Particle Size [§]		(b) (4)
(b) (4)		

Initial Quality/CMC Assessment
ONDQA

DRUG PRODUCT SPECIFICATION

Specification Established for Ezetimibe + Atorvastatin Tablet

Tests	Acceptance Criteria	Procedure
Appearance (release and shelf-life)	<p>10 mg/ 10 mg: White to off-white, capsule shaped, biconvex, film coated tablet with “320” on one side and plain on the other</p> <p>10 mg/ 20 mg: White to off-white, round, biconvex, film coated tablet with “321” on one side and plain on the other</p> <p>10 mg/ 40 mg: White to off-white, oval, biconvex, film coated tablet with “322” on one side and plain on the other</p> <p>10 mg/ 80 mg: White to off-white, capsule shaped, biconvex, film coated tablet with “323” on one side and plain on the other</p>	Test by visual observation
Assay – Atorvastatin (release and shelf-life)	(b) (4)	
Assay – Ezetimibe (release and shelf-life)		
Content Uniformity (release)		
Dissolution (release and shelf-life)		

Initial Quality/CMC Assessment
ONDQA

Ezetimibe/Atorvastatin FDC Tablet Specification

Tests	Acceptance Criteria	Procedure
Degradates – Atorvastatin (release)	(b) (4)	
Degradates – Atorvastatin (shelf-life)		
Degradates – Ezetimibe (release and shelf-life)		
Identity (release) HPLC UV		
Moisture (release)		

Initial Quality/CMC Assessment
ONDQA

**PRODUCT QUALITY
FILING REVIEW FOR NDA (ONDQA)**

NDA Number: 200153	Established/Proper Name: ezetimibe/atorvastatin
Applicant: MSP Singapore	Stamp Date: 29-APR-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On initial overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
B. facilities*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		

Initial Quality/CMC Assessment ONDQA

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	x		
D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Has an environmental assessment report or categorical exclusion been provided?	x		
13.	Does the section contain a description of the DS manufacturing process?	X		
14.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
15.	Does the section contain information regarding the characterization of the DS?	X		
16.	Does the section contain controls for the DS?	X		
17.	Has stability data and analysis been provided for the drug substance?	X		
18.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	
19.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	

Initial Quality/CMC Assessment
ONDQA

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
20.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
21.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
22.	Is there a batch production record and a proposed master batch record?	x		
23.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
24.	Have any biowaivers been requested?			See Biopharm filing memo
25.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
26.	Does the section contain controls of the final drug product?	x		
27.	Has stability data and analysis been provided to support the requested expiration date?	x		Review issue: whether data and analysis are adequate to support expiry
28.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
29.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	
F. methods validation (Mv)				
	Parameter	Yes	No	Comment
30.	Is there a methods validation package?	x		
G. microbiology				
	Parameter	Yes	No	Comment
31.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?			Non-sterile solid oral dosage form.
H. master files (DMF/MAF)				
	Parameter	Yes	No	Comment
32.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		
I. Labeling				
	Parameter	Yes	No	Comment
33.	Has the draft package insert been provided?	x		
34.	Have the immediate container and carton labels been provided?	x		
J. filing conclusion				
	Parameter	Yes	No	Comment
35.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	x		
36.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
37.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

{See appended electronic signature page}

Su (Suong) Tran
CMC Lead, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

{See appended electronic signature page}

Ali Al Hakim
Branch Chief, Office of New Drug Quality Assessment

Date *{see appended electronic signature page}*

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

/s/

SUONG T TRAN
06/27/2011

ALI H AL HAKIM
06/27/2011

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Division of Metabolism and Endocrinology Products

NDA: 200153

Applicant: MSP Singapore Co., LLC
(joint venture between Merck & Co., Inc. and
Schering Corp.)

Stamp Date: 02-SEP-2009

PDUFA Date: [not yet determined]

Proposed Proprietary Name: (b) (4)

Established Name: Ezetimibe/atorvastatin calcium

Dosage form and strength: Immediate release tablet –
10/10, 10/20, 10/40, and 10/80 mg/mg
ezetimibe/atorvastatin (free acid)

Route of Administration: oral

Indications: Treatment of hypercholesterolemia

PAL: Su (Suong) Tran, Branch II/DPA I/ONDQA

ONDQA Fileability: No

Filing deficiencies to be communicated to the Applicant:

1. You indicate that the manufacturing and testing facilities are currently not ready for GMP inspections. Therefore, this NDA is considered to be incomplete and cannot be filed until all facilities involved in the manufacturing and testing of the commercial product are ready for GMP inspections.
2. Provide the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54.
3. Your primary stability batches were manufactured at an R&D facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data as well as multipoint dissolution profiles.)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	A consult review of the biowaiver request for the 10/40 dosage strength will be requested of the ONDQA Biopharmaceutics Review Staff.
CDRH or CBER	<i>Not Applicable</i>
EA	Categorical exclusion request will be assessed by Primary Reviewer.
EES	Facilities are not ready for inspection: reason for the recommendation to not file the NDA until all facilities are ready for inspection.
OSE	<i>Labeling consult request will be sent as part of DMEP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>Not Applicable</i>
Pharm/Tox	<i>Not Applicable: No impurity/degradant exceeds applicable ICH qualification thresholds.</i>

Summary: [See the discussion in Critical Issues later in this review.]

This is an electronic NDA, filed as a 505(b)(2) application, with the reference listed drug (RLD) being Lipitor (atorvastatin calcium) from a different applicant (Pfizer). It should be noted that the RLD is crystalline atorvastatin and this new combination product has amorphous atorvastatin.

Reference is made to the approved NDA 21445 (same applicant: MSP Singapore) for all CMC information on the ezetimibe drug substance. Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance.

The product is a fixed dose combination, immediate-release (b) (4) tablet available in the strengths of 10/10, 10/20, 10/40, and 10/80 mg/mg ezetimibe/atorvastatin (free acid). In support of efficacy, a pivotal bioequivalence (BE) study, Protocol 145, was conducted to compare the combination tablet to the concomitantly administered individual approved Zetia (ezetimibe) and Lipitor (atorvastatin) for the dosage strengths 10/10, 10/20, and 10/80 mg/mg ezetimibe/atorvastatin (free acid). A biowaiver request is made for the 10/40 dosage strength.

Maximum daily dose is 10/80 mg/mg ezetimibe/atorvastatin (free acid).

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CRITICAL ISSUES

Has all information requested during the IND phases and at the pre-NDA meeting been included?

FDA's 30-JUN-2009 letter:

The 505(b)2 approval pathway may be used for a fixed dose combination product that is sufficiently similar to an approved product to permit reliance, where scientifically justified, on certain existing information which includes FDA's finding of safety and/or effectiveness for an approved drug product. An assessment of similarity between a proposed product and an approved product may include comparative physicochemical and biological studies, bridging toxicology, pharmacokinetic, pharmacodynamic and clinical data as appropriate. It is recommended that the physicochemical characteristics of the atorvastatin used in the combination toxicology studies, the atorvastatin to be used in your FDC product, and the atorvastatin used in Lipitor be thoroughly compared. Additional analytical characterization may be required on one or more of these substances if these data are not currently available. If these data can not be supplied or the data show that there are significant differences in impurity profiles between these three versions of atorvastatin, a bridging toxicology study in a single species may be required for marketing approval in the United States.

Reviewer's comment: No comparative physicochemical data was included in the initial NDA submission as requested by FDA to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. After FDA reiterated the request for this information on 28-SEP-2009, the applicant submitted comparative impurity results on 05-OCT-2009 for the RLD Lipitor and the FDC products. Limits on the atorvastatin-related impurities in the FDC product are lower than the ICH qualification threshold (as applicable to the maximum daily dose) with the exception of the limit on (b) (4) (b) (4) for 10 mg atorvastatin), which is adequate as per ICH guidelines for an inactive metabolite. While the comparative impurity results are complete for further review, the applicant should submit additional physicochemical data as requested by FDA on 30-JUN-2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. This information is required in support of the 505(b)(2) application.

CMC-related consults:

- A consult review of the biowaiver request for the 10/40 dosage strength will be requested of the ONDQA Biopharmaceutics review staff.
- A consult review of the manufacturing process and its development will be requested of the ONDQA manufacturing science review staff.

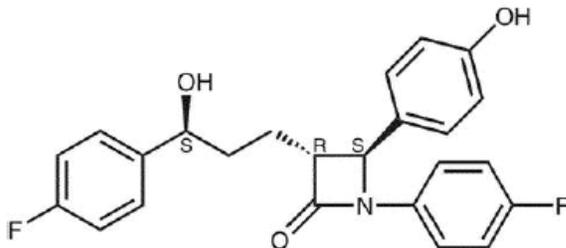
Critical issues: To be discussed in the following sections.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Drug substance:

Ezetimibe

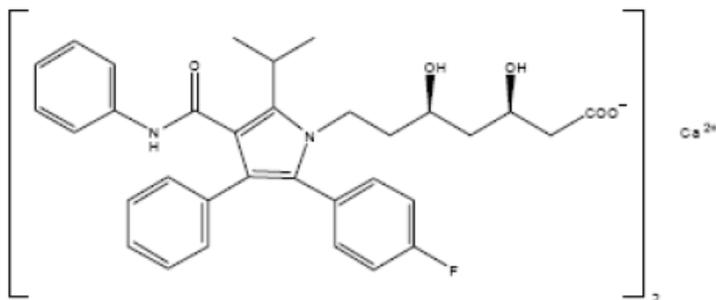
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature [Ref. 5.4: 4290].

Atorvastatin

Atorvastatin calcium is [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1).. The empirical formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca$ and its molecular weight is 1155.36. Its structural formula is:



Atorvastatin calcium is a white to off-white powder that is very slightly soluble in water, insoluble in acetonitrile, and soluble in methanol [Sec. 3.2].

Critical Issues:

Reference is made to the approved NDA 21445 for all CMC information on the ezetimibe drug substance. No issue should be found for ezetimibe because the information is approved in NDA 21445 (the applicant will be reminded that only the approved information can be referenced).

Reference is made to the DMF 18468 for all CMC information on the atorvastatin calcium (amorphous) drug substance. No specific comment regarding atorvastatin calcium (amorphous) can be discussed in this review because the CMC information is in a DMF. The primary reviewer will review any information in the DMF that has not been evaluated. The drug substance specifications are copied on pages 20-23 of this review. Because different polymorphs of atorvastatin may have different in vivo profiles, the reviewer will evaluate the adequacy of the proposed X-ray powder diffraction test and acceptance criteria used to assure consistent polymorphic quality of this drug substance.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Drug product

The composition of the drug product is copied below.

Ezetimibe (+) Atorvastatin Tablet – Market Composition

Components	Compendial Testing	Function	Unit Strength (Ezetimibe/Atorvastatin)			
			10/10 mg/mg	10/20 mg/mg	10/40 mg/mg	10/80 mg/mg
(b) (4)						
Ezetimibe (SCH58235) (b) (4)	---	Active	mg/tablet 10.00			
Atorvastatin Calcium [§] (amorphous) (equivalent free acid) (b) (4)	---	Active	10.34 (10.00)	20.68 (20.00)	41.36 (40.00)	82.73 (80.00)
Film-Coating: (b) (4)						
Total Coated Tablet Wt.:			624.1 mg	364.1 mg	519.8 mg	830.4 mg (b) (4)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. The biowaiver request for the 10/40 strength will be reviewed by the ONDQA Biopharmaceutics review staff.
- **Established name and dosage strength.** The proposed established names of the product are “ezetimibe” and “atorvastatin”, which are acceptable because they correlate with the dosage strength as per current CDER policy on nomenclature. The drug substances are ezetimibe and atorvastatin calcium. The dosage strength for atorvastatin is based on the free acid.
- **Comparability of the product used in the clinical studies, stability studies, and commercial product.** The applicant states that the formulation is the same for the pivotal clinical batches, primary stability batches, and commercial product.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Manufacturing process of the drug product



The flow diagram is copied on page 26 of this review.

Critical Issue: Comparability of the product used in the clinical studies, stability studies, and commercial product. The applicant indicates that the manufacturing process of the pivotal biobatch and primary stability batches “was representative and at least 1/10th the size of the commercial manufacturing process” (see copied table on the next pages). They were manufactured at the Merck R&D site in West Point, PA. The applicant includes a comparison of equipment used at the R&D and commercial sites (copied on the next pages). As per FDA’s request for information on 29-SEP-2009, the applicant confirmed on 05-OCT-2009 that “the proposed manufacturing process (equipment, environmental controls and in-process controls) for the to-be-marketed product as described in Sec. 3.2.P.3.3 and 3.2.P.3.4 is the same as that used for the batches in the bioequivalence study and the formal stability studies. The only minor difference described in Sec. 3.2.P.2.3.2.5 is that the [redacted] (b) (4) [redacted] was changed post-manufacture of the biobatches. The composition of all clinical and formal stability batches is the same as the to-be-marketed product.” No proposed or actual master production record for the manufacture of the commercial product can be located in the NDA, and this information is required for a 505(b)(2) application as per 21 CFR 314.54. All disciplines in the review team were notified that the pivotal biobatches were manufactured at an R&D facility. This issue may have a direct impact on the ClinPharm review because 21 CFR 320.25(i)(2) (regarding bioavailability/bioequivalence studies) requires that “Samples of the drug product to be tested shall be manufactured using the same equipment and under the same conditions as those used for full-scale production.” The applicant has not submitted multipoint dissolution profiles comparing these clinical batches and the to-be-marketed product even though FDA requested for the data on 29-SEP-2009.

The primary CMC reviewer will evaluate all available information to determine whether the R&D manufacturing process adequately simulates the commercial process in order to establish the expiry of the commercial product based on data of the primary stability batches.

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Comparison of Formal Stability Batch Sizes and Production Scale Batch Sizes

Formulation	Unit Operation Batch Size	FSS (biobatch bolded)	Production Scale	
			Min	Max
(b) (4)				

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Comparison of Equipment Used for the Primary Stability Batches and Production
Batches for Ezetimibe + Atorvastatin Tablet

Unit Operation	Process Equipment	
	Primary Stability Batches [†] – Merck, West Point, PA	Production Facilities - as specified in Sec. 3.2.P.3.1-0653c-tablet
(b) (4)		

Development of the manufacturing process. This reviewer recommends that the manufacturing section of the NDA, including the developmental information, be reviewed by the ONDQA Manufacturing Science review staff. (b) (4)

(b) (4)

Drug product specification

The proposed drug product specification is copied on pages 27-28 of this review.

Critical Issues:

- **Characterization of impurities.** Reference is made to the DMF (b)(4) for information on impurities of atorvastatin calcium and to the approved NDA 21445 for information on impurities of ezetimibe. The drug product has atorvastatin-specific degradants as tabulated below. Their structures are included in the NDA.

Atorvastatin Impurities

Sec. 3.2.P.5.2.1-0653c-tablet (Atorvastatin Assay by HPLC)	Impurity Name	Primary Mechanism
(b)(4)		

- **Limits on degradation products.** The only degradant related to ezetimibe is (b)(4) with a limit of (b)(4) which is below the ICH identification threshold. The atorvastatin-related degradants are copied in the table above. The limits on (b)(4) (b)(4) for 10 mg and (b)(4) for the higher dosage strengths), (b)(4) and (b)(4) are less than the ICH qualification threshold of 0.5% for a maximum daily dose of 80 mg atorvastatin. The limits on (b)(4) are (b)(4) for the 10 mg atorvastatin and (b)(4) for the higher dosage strengths, which are qualified as per ICH guidelines for an impurity that is also an inactive metabolite of the drug substance. A limit is proposed on the sum of (b)(4) and (b)(4) because these impurities interconvert in the presence of water in the test method diluent, with the dominant one being (b)(4). The limit of the sum is (b)(4) which is less than the ICH qualification threshold of 0.5% for each impurity.
- **Moisture content.** The (b)(4) of atorvastatin increases when this drug substance is exposed to moisture. However, the increase in moisture content should not be an issue because the packaging includes a desiccant and oxygen scavengers. The reviewer will evaluate the adequacy of the proposed limits ((b)(4) and (b)(4) for the 10 mg and higher dosage strengths, respectively) based on all available data.

Container closure systems for product distribution

The tablets of all dosage strengths will be packaged in the same commercial container closure system: 10-tablet blisters, each enclosed a child-resistant plastic case and over-wrapped in a foil pouch with two oxygen scavengers and a desiccant.

The drug product will be packaged in a vented (b)(4) blister with push-through aluminum lidding. The (b)(4) aluminum blister card is enclosed in a (b)(4) plastic case (for child-resistance) which is contained in a (b)(4) aluminum pouch along with two oxygen scavengers and one (b)(4) desiccant canister. The aluminum pouch is composed of (b)(4) (b)(4) Information on the formable blister material, lidding, foil pouch and (b)(4) case can be found in [Table 3.2.P.7-0653c-tablet: 1], [Table 3.2.P.7-0653c-tablet: 2], [Table 3.2.P.7-0653c-tablet: 3] and [Table 3.2.P.7-0653c-tablet: 4], respectively.

Venting of the blister card allows for the free exchange of oxygen and moisture between the tablet contained in the blister cavity and the oxygen scavenger and desiccant contained in the foil pouch. The oxygen scavengers and desiccant contained in the aluminum pouch provide the proper environment for the product over the proposed shelf-life.

A range of tablet counts, (b)(4) is supported for the sample and trade packages. A single-tablet Hospital Unit Dose (HUD) package is also supported. As child-resistance is not required for this hospital package or for sample packages, the (b)(4) case is not utilized in those cases.

Critical Issues:

- **Sample and hospital packaging.** The commercial product will be packaged in a 10-tablet blister. It appears that the sample packaging (? tablets/blister) and hospital packaging (one-tablet/blister) will have a different tablet count per blister. The applicant should clarify whether the materials of construction are the same for all packaging systems and indicate the different tablet counts in the sample packaging.
- **Protective properties of the complete packaging system.** The applicant proposes to include oxygen scavengers and a desiccant in the secondary packaging system (foil pouch) as well as a vented primary packaging system (blister) to address the oxygen- and moisture- sensitive nature of atorvastatin. The reviewer will confirm that the complete packaging system can adequately protect the product through its shelf life, and that adequate instructions are included in the

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

labeling for the storage of the product in the intact (i.e., sealed) foil pouch. Once the patient opens the foil pouch, an in-use shelf life of 30 days is proposed (see the Stability discussion later in this review.)

- **Information on the primary packaging components.** The applicant identifies the product-contact surfaces to be the (b) (4) blister film and the aluminum lidding foil (b) (4). References to the CFR for their components are provided, which will be confirmed by the reviewer. Samples of the container closure systems, including the vented blister, plastic case, and foil pouch, will be obtained from the applicant. They will assist the reviewer in determining whether the product may come into contact with any other component, given that the (b) (4) blister film is “vented” through what it appears to be perforations in the film.

- [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Stability of the drug product

8.1.1 Stability Summary and Conclusions

The stability of Ezetimibe (+) Atorvastatin Tablet is presented as a compilation of data generated from the Formal Stability Studies (FSS), which have been conducted in accordance with ICH Guidelines. Up to 26 weeks of formal stability data are included in this application.

The Formal Stability Studies indicate satisfactory stability of the product in package for 26 weeks at the long term storage condition of 25°C/60%RH and the accelerated condition of 40°C/75%RH. No significant changes were observed at any storage condition. Fifty-two weeks at 25°C/60%RH and 26 weeks at 40°C/75%RH of supportive stability testing is available on the core tablet formulation (without film coat). These data serve as a valuable indicator to the long term performance of the FSS studies because the batches are un-desiccated and therefore represent a worst case from a stability standpoint. Data generated at the 39 and 52 week time points of the FSS (primary stability) will be available to the agency during the first 6 months of regulatory review.

Based on the data presented, the proposed stability updates and the corresponding evaluations, the applicant proposes an initial shelf life of 24 months for Ezetimibe (+) Atorvastatin Tablet when stored at 20-25°C (68-77°F). This shelf life may be extended based on additional data that would be provided to the agency via an appropriate regulatory submission.

The product package provides protection from light, moisture, and oxygen. Therefore, it is recommended to store tablets in the original foil pouch until use. After the foil pouch is opened, protect from moisture and light, store in a dry place and discard unused tablets after 30 days.

Critical Issues:

- Three batches of each of the 10/10, 10/20, and 10/80 mg/mg ezetimibe/atorvastatin were designated primary stability batches. The 10/40 strength was bracketed (b) (4) and will be packaged in the same container closure systems. One stability batch of each strength was also a biobatch in the pivotal BE studies (see table on page 24).
- As discussed earlier in this review, the primary stability batches were manufactured with the commercial formulation, within 1/10th of the maximum commercial scale, and at an R&D facility. The applicant includes a comparison of scales and equipment used at the R&D and commercial sites (see tables on pages 8-9) and a discussion of process development in order to link the R&D manufacturing to the commercial manufacturing. As the standard requirement, the applicant should submit stability data to bridge the R&D manufacturing to the commercial

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

manufacturing: for this new FDC product: three batches with three months of accelerated data and multipoint dissolution profiles.

- The packaging used for the stability batches is not identical to that of the commercial product. The stability batches were packaged [REDACTED] (b) (4) [REDACTED]. The commercial product will have one 10-tablet blister in one foil pouch containing two (b) (4) oxygen scavengers and one (b) (4) desiccant. The applicant states that all both packaging systems have the “same materials of construction”. The primary CMC reviewer will evaluate all available information to determine whether the R&D manufacturing process and stability packaging adequately simulate the commercial process and packaging in order to establish the expiry of the commercial product based on data of the primary stability batches.
- The packaging system consists of oxygen scavengers and a desiccant in the secondary packaging system (foil pouch) as well as a vented primary packaging system (blister) to address the oxygen- and moisture- sensitive nature of atorvastatin. As discussed earlier in this review, the reviewer will confirm that the complete packaging system can adequately protect the product through its shelf life, and that adequate instructions are included in the labeling for the storage of the product in the intact (i.e., sealed) foil pouch. Once the patient opens the foil pouch, an in-use shelf life of 30 days is proposed, and the applicant includes data in support of this in-use period. The reviewer will evaluate the data and confirm that adequate instructions are included in the labeling for this in-use shelf life.
- The NDA is submitted with 26 weeks of stability data at the long term storage condition of 25 °C/60% RH and at the accelerated condition of 40 °C/75% RH. The applicant proposes to submit an amendment within 6 months of the review cycle with 39-week and 52-week stability data. The following standard statement will be conveyed to the applicant “A complete NDA should be submitted with at least 12-month primary stability data at the long term storage condition. While we may attempt to review unsolicited amendments submitted during the review cycle, the review of such amendments will depend on the timeliness of the submission, extent of the submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and Practices (GRMPPs) timelines, we cannot guarantee that we will review unsolicited amendments such as your proposed stability update.”

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Supporting NDA or IND:

IND 101953: same sponsor

NDA 21445 Zetia (ezetimibe): same applicant

Supporting DMF:

DMF	TYPE	HOLDER	ITEM REFERENCED	LOA
(b) (4)	II			X
	III			
	III			x

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

GMP facilities:

EER has not been sent to the Office of Compliance because the facilities are not ready for inspection as indicated by the applicant below.

Manufacturing Sites Listed in the NDA

Drug Substance - Ezetimibe
<u>Manufacturing, Packaging, Release and Stability Testing:</u> Schering-Plough LTD, Singapore Branch 50 Tuas West Drive Singapore 638408 Establishment Registration No. 3002808083 Facility will be Pre-Approval Inspection ready by 30Nov2009. Contact: Douglas Sottos Director of Quality Phone: 65-6869-8520

Drug Substance – Atorvastatin
<u>Manufacturing, Packaging, Release and Stability Testing:</u> Dr. Reddy's Laboratories Limited Chemical Technical Operations – Unit-II Plot No. 110 & 111 Sri Venkateswara Co-operative Industrial Estate Bollaram, Jinnaram Medak District Andhra Pradesh India 502325 Establishment Registration Number: 3005448030 Facility will be Pre-Approval Inspection ready by 01Oct2009. Contact: J. Shravan Reddy Sr. Manager – Project Management Phone: 91 040 2304 5439 Ext-643

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

MANUFACTURING SITES LISTED IN THE NDA (Cont.)

Drug Product
<p>Manufacturing: Ezetimibe (b) (4)</p> <p>Schering-Plough Products Las Piedras Operations Pridco Industrial Park State Road #183 LasPiedras, Puerto Rico 00771 Establishment Registration No. 2650155</p> <p>Facility will be Pre-Approval Inspection ready by 30Nov2009. Contact: Genoveva Yordan Director, Quality Operations Phone: 787-912-2004 or Osvaldo Lozada Manager, Quality Audits Phone: 787-912-2112</p>
<p>Manufacturing: Ezetimibe (b) (4)</p> <p>Schering Plough (Singapore) Pte Ltd 70 Tuas West Drive Singapore 638414 Establishment Registration No. 3004199021</p> <p>Facility will be Pre-Approval Inspection ready by 30Nov2009. Contact: Douglas Sottos Director of Quality Phone: 65-6869-8520</p>
<p>Manufacturing: Atorvastatin (b) (4)</p> <p>Merck Sharp & Dohme Technology (Singapore) Pte. Ltd. 21 Tuas South Avenue 6 Singapore 637766 Establishment Registration No. 3003431146</p> <p>Facility will be Pre-Approval Inspection ready by 31Dec2009. Contact: Michael Brian McGuinness Director, Quality Operations Phone: 65-6880-5252</p>

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

MANUFACTURING SITES LISTED IN THE FDA (CONT.)

Drug Product (cont.)
<p><u>Manufacturing:</u> [REDACTED] (b) (4)</p> <p>Merck Sharp & Dohme Quimica de Puerto Rico Ltd. Road #2, Kilometer 60.3 Sabana Hoyos Arecibo PR 00688 Establishment Registration No. 2650235</p> <p>Facility will be Pre-Approval Inspection ready by 31Dec2009. Contact: Alvin Lopez de Victoria Director, Quality Operations Phone: 787-623-7387</p>
<p><u>Manufacturing: Atorvastatin</u> [REDACTED] (b) (4)</p> <p>Patheon Pharmaceuticals Inc. 2110 E. Galbraith Rd. Cincinnati, OH 45237-1625 USA FEI 1510437</p> <p>Facility will be Pre-Approval Inspection ready by 15Dec2009. Contact: David Leuck Director, Quality Operations Phone: 513-948-6358</p>
<p><u>Packaging</u></p> <p>Anderson Packaging Inc. 4545 Assembly Drive Rockford IL 61109</p> <p>Facility will be Pre-Approval Inspection ready by 15Dec2009. Contact: Mitchell Farris Director, Quality Phone: 815-484-8967</p>
<p><u>Packaging, Stability Testing</u></p> <p>Merck & Co., Inc 4633 Merck Road Wilson, North Carolina 27893 USA Establishment Registration No. 1036761</p> <p>Facility will be Pre-Approval Inspection ready by 31Dec2009. Contact: Ms. Pam Mills Director, Wilson Quality Operations Phone: 252-246-6379</p>

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Sites Used During Development

Drug Substance – Atorvastatin

Analytical Development

Merck & Co., Inc.
126 E. Lincoln Avenue
Rahway, NJ 07065, USA
Establishment Registration No. 2211017

Facility will be Pre-Approval Inspection ready by 31Dec2009.

Contact: Mr. Gerard Lohan
Executive Director, GMP Quality – Commercialization and Early Development
Phone: 215-652-6070

Drug Product

Process and Analytical Development, Manufacturing, Release Testing, and Stability Monitoring and Testing

Merck and Co., Inc.[†]
770 Summeytown Pike
West Point, PA 19486-0004, USA
Establishment Registration No. 2510592

[†]Responsible for the Merck dedicated laboratory at Pharmaceutical Manufacturing Research Services, Inc. (PMRS) and any contract facilities used during development.

Facility will be Pre-Approval Inspection ready by 31Dec2009.

Contact: Mr. Gerard Lohan
Executive Director, GMP Quality – Commercialization and Early Development
Phone: 215-652-6070

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

DRUG SUBSTANCE SPECIFICATION

Ezetimibe Specification

Test	Acceptance Criteria
Description [†]	White powder
Identification	(b) (4)
Infrared Spectrum [†] (SCH 58235)	
Chiral HPLC (b) (4)	
Moisture (KF) [†]	
Specific Rotation ([α] _D 20, 10 mg/mL in methanol)	
Heavy Metals	
Sulfated Ash	
Assay (Achiral HPLC) [†]	
Related Compounds	
Achiral Related Compounds [†]	
(b) (4)	

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Test	Acceptance Criteria
(b) (4)	
Particle Size† Release Shelf Life	(b) (4)
† These tests are required for recertification testing.	

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Atorvastatin Calcium (amorphous) Specification

Test	Specification
Description	White to off-white colored powder, free from visible extraneous matter
Identification	(b) (4)
IR-Spectrum	
Test for calcium	
Solubility	
Water by KF	
Heavy Metals	
Related Substances by HPLC	
Assay by HPLC (on anhydrous basis)	

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

(b) (4)

(b) (4)

Specific optical rotation (on anhydrous basis)

Calcium content by titrimetry (on anhydrous basis)

X-ray Powder Diffraction pattern

Particle Size[†]

[†]Testing specific to Ezetimibe (+) Atorvastatin Tablet

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

BATCH INFORMATION

10/10 dosage strength:

Batch number	WL00031196 ^{II}	WL00031690	WL00031691
Use	Stability	Biobatch/Stability	Stability
Drug Substance Batches			
Ezetimibe	080300800	080200484	080200485 (b) (4)
	[REDACTED]		
Atorvastatin Calcium	ABBH003996	ABBH004055 (b) (4)	ABBH003996/ ABBH004055 (b) (4)
	[REDACTED]		
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA
Theoretical batch size (tablets)	[REDACTED] (b) (4)		
Manufacturing date	Sep 2008	Sep 2008	Sep 2008

10/20 dosage strength:

Batch number	WL00031197	WL00031693	WL00032969
Use	Biobatch/Stability	Stability	Stability
Drug Substance Batches			
Ezetimibe	080300800	080200485	080200484 (b) (4)
	[REDACTED]		
Atorvastatin Calcium	ABBH003996 (b) (4)	ABBH003996/ ABBH004055 (b) (4)	ABBH005576 (b) (4)
	[REDACTED]		
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA
Theoretical batch size (tablets)	[REDACTED] (b) (4)		
Manufacturing date	Sep 2008	Sep 2008	Feb 2009

10/40 dosage strength:

Batch number	WL00034555
Use	Biobatch
Drug Substance Batches	
Ezetimibe	080300800 (b) (4)
	[REDACTED]
Atorvastatin Calcium	ABBH005576 (b) (4)
	[REDACTED]
Drug Product Manufacturing Site	West Point, PA (b) (4)
Theoretical batch size (tablets)	[REDACTED]
Manufacturing date	May 2009

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

10/80 dosage strength:

Batch number	WL00031198	WL00031694	WL00031695
Use	Biobatch/Stability	Stability	Stability
Drug Substance Batches Ezetimibe	080300800	080200484	080200485 (b) (4)
Atorvastatin Calcium	ABBH003996	ABBH004055 (b) (4)	ABBH003996/ ABBH004055 (b) (4)
Drug Product Manufacturing Site	West Point, PA	West Point, PA	West Point, PA (b) (4)
Theoretical batch size (tablets)			
Manufacturing date	Sep 2008	Sep 2008	Sep 2008

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

DRUG PRODUCT MANUFACTURE



(b) (4)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

DRUG PRODUCT SPECIFICATION

Specification Established for Ezetimibe + Atorvastatin Tablet

Tests	Acceptance Criteria	Procedure
Appearance (release and shelf-life)	<p>10 mg/ 10 mg: White to off-white, capsule shaped, biconvex, film coated tablet with “320” on one side and plain on the other</p> <p>10 mg/ 20 mg: White to off-white, round, biconvex, film coated tablet with “321” on one side and plain on the other</p> <p>10 mg/ 40 mg: White to off-white, oval, biconvex, film coated tablet with “322” on one side and plain on the other</p> <p>10 mg/ 80 mg: White to off-white, capsule shaped, biconvex, film coated tablet with “323” on one side and plain on the other</p>	Test by visual observation
Assay – Atorvastatin (release and shelf-life)	(b) (4)	
Assay – Ezetimibe (release and shelf-life)		
Content Uniformity (release)		
Dissolution (release and shelf-life)		

Initial Quality Assessment

Pre-Marketing Assessment Division 1 Branch 2

Tests	Acceptance Criteria	Procedure (b) (4)
Degradates – Atorvastatin (release)		
Degradates – Atorvastatin (shelf-life)		
Degradates – Ezetimibe (release and shelf-life)		
Identity (release) HPLC UV		
Moisture (release)		

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? NO

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	x		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	x		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?			Many manufacturing sites, including the drug product manufacturer, are not ready for the GMP inspection until 31-DEC-2009.
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		Exclusion request per 21 CFR 25.31 is included.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	x		By reference to other submissions.
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	x		
7	If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?			Requested information cannot be located in NDA.
8	Have draft container labels and package insert been provided?	x		
9	Have all DMF References been identified?	x		
10	Is information on the investigational formulations included?	x		
11	Is information on the methods validation included?	x		
12	If applicable, is documentation on the sterilization process validation included?			Not applicable.

Comments to the Applicant: (next page)

Initial Quality Assessment
Pre-Marketing Assessment Division 1 Branch 2

Comments to the Applicant:

[Note to Reviewers: These comments to the Applicant do not include all the critical issues discussed in this IQA/filing review. Certain issues are for the primary reviewer's consideration and do not necessitate comments to the Applicant in the 74-day letter.]

Filing deficiencies:

1. You indicate that the manufacturing and testing facilities are currently not ready for GMP inspections. Therefore, this NDA is considered to be incomplete and cannot be filed until all facilities involved in the manufacturing and testing of the commercial product are ready for GMP inspections.
2. Provide the proposed or actual master production record for the manufacture of the commercial product in support of your 505(b)(2) application as per 21 CFR 314.54.
3. Your primary stability batches were manufactured at an R&D facility. Provide stability data to bridge the R&D manufacturing to the commercial manufacturing (i.e., data for three commercial batches with at least three months of long term and accelerated data as well as multipoint dissolution profiles.)

Other comments that are not filing deficiencies:

1. We remind you that, regarding the reference to CMC information in NDA 21445 Zetia, only the approved information can be referenced.
2. Provide samples of the container closure system, including the vented blister, plastic case, and foil pouch.
3. Clarify whether the materials of construction are the same for all packaging systems (commercial, hospital use, and sample) and indicate the tablet counts in the sample packaging.
4. A complete NDA should be submitted with at least 12-month primary stability data at the long term storage condition. Your NDA is submitted with 26 weeks of stability data at the long term storage condition of 25 °C/60% RH and at the accelerated condition of 40 °C/75% RH. While we may attempt to review unsolicited amendments submitted during the review cycle, the review of such amendments will depend on the timeliness of the submission, extent of the submitted data, and available resources. Therefore, in accordance with Good Review Management Principles and Practices (GRMPPs) timelines, we cannot guarantee that we will review unsolicited amendments such as your proposed stability update.
5. Your primary stability batches and clinical batches used in the pivotal bioequivalence studies were manufactured at an R&D facility. Provide multipoint dissolution profiles comparing these batches and the to-be-marketed product.
6. In addition to the comparative impurity results submitted in your 05-OCT-2009 communication, provide physicochemical data as requested by FDA on 30-JUN-2009 to compare the atorvastatin used in the toxicology studies, the atorvastatin used in the commercial product, and the atorvastatin used in the RLD Lipitor. This information is required in support of the 505(b)(2) application.

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

/s/

SUONG T TRAN
10/07/2009

ALI H AL HAKIM
10/07/2009