

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

CHEMISTRY REVIEW(S)

NDA 21-687

Vytorin (Ezetimibe/Simvastatin Tablets)

MSP Singapore

**Sharon L. Kelly
Metabolic and Endocrine
HFD 510**



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.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment.....	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE [Name, Manufacturer].....	12
P DRUG PRODUCT [Name, Dosage form].....	13
A APPENDICES	103
R REGIONAL INFORMATION	114
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	114
A. Labeling & Package Insert	114
B. Environmental Assessment Or Claim Of Categorical Exclusion	116
III. List Of Deficiencies To Be Communicated.....	116

Chemistry Review Data Sheet

1. NDA 21-687
2. REVIEW #: 1
3. REVIEW DATE: July 08, 2003
4. REVIEWER: Sharon Kelly
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

24-SEP-2003

Amendment

06-NOV-2003

Amendment

13-NOV-2003

Amendment

12-FEB-2004

Amendment

13-APR-2004

Amendment

20-APR-2004

Amendment

23-APR-2004

Amendment

26-MAY-2004

Chemistry Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name: MSP Singapore Company, LLC
Address: 300 Beach Road # 12-08
The Concourse
Singapore 199555
Representative: Diane Louie, M.D., M.P.H.
Telephone: 732 - 594 - 7186

MSP Singapore Company, LLC (MSP) is a joint venture between Merck & Co., Inc. and Schering Corporation. Merck Research Laboratories (MRL), a Division of Merck & Co., on behalf of MSP, is the primary point of contact for the ezetimibe/simvastatin combination tablet program. The Representative is as listed above.

8. DRUG PRODUCT NAME/CODE/TYPE: VYTORIN
(ezetimibe/simvastatin combination tablet)

- a) Proprietary Name: VYTORIN
- b) Non-Proprietary Name (USAN): ezetimibe/simvastatin combination tablet
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 USC Sec. 505 (b)(1)
NDA 21-445 ZETIA (ezetimibe) Schering-Plough
NDA 19-766 ZOCOR (simvastatin) Merck & Co., Inc.

10. PHARMACOL. CATEGORY: Primary Hypercholesterolemia and
Homozygous Familial Hypercholesterolemia

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: ezetimibe 10mg and simvastatin 10mg, 20mg,
40mg or 80mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: XX Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

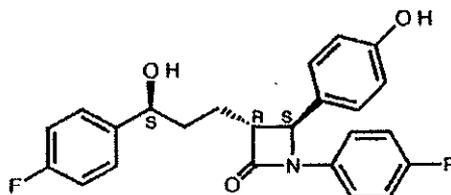
Chemistry Assessment Section

_____ SPOTS product – Form Completed

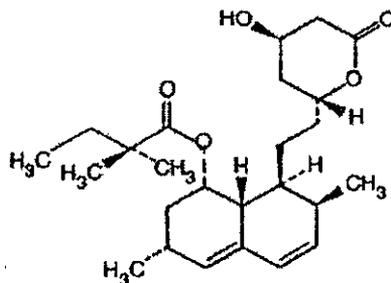
 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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



Simvastatin [1S-[1 α ,3 α ,7 β ,8 β (2S*,4S*),8 β]-1,2,3,7,8,8a-Hexahydro-3,7-dimethyl -8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl) ethyl]-1-naphthalenyl-2,2-dimethylbutanoate



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
1	III	— —		4	N/A		
	III	—		4	N/A		



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		
III		4	N/A		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

Chemistry Assessment Section

- 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
IND	65,066	MK-0653A, ezetimibe/simvastatin combination tablet
IND	52,791	ezetimibe
IND	25,742	MK-0733, simvastatin
NDA	21-445	Zetia
NDA	19-766	Zocor

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending, June 19, 2004		
Methods Validation	Pending Approval		
ODS / DMETS	Labeling revisions. Proprietary name Vytorin™ acceptable	22-MAR-2004	Jinhee Jahng, Pharm.D.
EA	N/A Categorical Exclusion Requested under 21 CFR § 25.31(b).		
Microbiology	N/A		

The Chemistry Review for NDA 21-687

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA application can be Approved from a chemistry review perspective.

Based on the stability data available to date, the Agency grants the Sponsor's proposed initial shelf-life of 24 months for ezetimibe/simvastatin combination tablets stored at 20-25°C (68-77°F). This shelf life may be extended in the future based on additional data that would be provided to the Agency. The EES report is Acceptable.

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

II. Summary of Chemistry Assessments

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

1. Drug Product

Ezetimibe and simvastatin are supplied as an immediate release, combination tablet for oral administration. Four new dosage forms containing a fixed dose of ezetimibe and a variable dose of simvastatin have been developed. Each tablet contains 10 mg of ezetimibe and 10, 20, 40, or 80 mg of simvastatin. Formulation development activities focused on developing a chemically and physically stable formulation that was bioequivalent to the co-administered ezetimibe and simvastatin monotherapy tablets, respectively.

Ezetimibe/simvastatin combination tablets may be marketed in the following container closure systems:

Ezetimibe 10 mg/Simvastatin 10 mg Combination Tablets

- 75 mL unit-of-use:  bottle with foil induction seals and child-resistant plastic closures and desiccant, 30 and 90 counts.
- 7 oz bulk  bottle with foil induction seals and non-child-resistant plastic closures and desiccant, 1000 count
- White Opaque:  blisters with push through aluminum lidding

Ezetimibe 10 mg/Simvastatin 20 mg Combination Tablets and Ezetimibe 10 mg/ Simvastatin 40 mg Combination Tablets

- 75 mL unit-of-use  bottle with foil induction seals and child-resistant plastic

Chemistry Assessment Section

closures and desiccant, 30 and 90 counts

- 14 oz bulk [redacted] bottle with foil induction seals and non-child-resistant plastic closures and desiccant, 1000 count for the 10mg/20mg strength and 500 count for 10mg/40mg strength
- White Opaque [redacted] blisters with push through aluminum lidding

Ezetimibe 10 mg/Simvastatin 80 mg Combination Tablets

- 75 mL unit-of-use [redacted] bottle with foil induction seals and child-resistant plastic closures and desiccant, 30 count
- 7 oz unit-of-use [redacted] bottle with foil induction seals and child-resistant plastic closures and desiccant, 90 count
- 20 oz bulk [redacted] bottle with foil induction seals and non-child-resistant plastic closures and desiccant, 500 count
- White Opaque [redacted] blisters with push through aluminum lidding

The ezetimibe/ simvastatin combination tablet manufacturing process is based on [redacted] technology. The manufacturing process consists of [redacted]. Process control setpoints are established for the [redacted] conditions. Commercial-scale development activities were completed at the [redacted] scale.

Process development studies were performed. The critical parameters of the drug product manufacturing process have been adequately examined with respect to their effect on batch reproducibility, product performance and/or quality. Appropriate operating ranges were established based on this data.

The manufacturing process impurities are sufficiently monitored. A specific High Performance Liquid Chromatography (HPLC) analytical method was developed to separate ezetimibe from process impurities, degradates, simvastatin, and simvastatin degradates. A gradient method was developed based on the need to resolve ezetimibe and [redacted], and to provide adequate selectivity for the degradation products specific to ezetimibe. Under the conditions of the method, ezetimibe elutes before its more [redacted] products, and it also elutes before simvastatin and [redacted]. Following elution of the [redacted] product, gradient changes elute simvastatin and its related compounds.

In addition, [redacted] method was developed to enable direct identification of ezetimibe and simvastatin from an intact combination tablet. A [redacted] general identity library has been generated for each potency of the ezetimibe/simvastatin combination tablet using samples from 3 lots of finished product.

A [redacted] method was also developed to measure the final moisture content ([redacted] endpoint), based on moisture data generated using Karl Fischer titration as the primary method. The final moisture content corresponds to the point where the moisture content of the [redacted] determined by Karl Fischer (KF), is approximately equal to the moisture content of the [redacted] formulation, determined by KF, prior to [redacted]. In principle the [redacted]; would be continued until all

Chemistry Assessment Section

ethanol and water added during the _____ was removed. _____; beyond this point may remove moisture bound to the excipients in the formulation. The moisture calibration equation was calculated using KF moisture results corrected for lactose-bound moisture as the reference data. With the correction for lactose-bound moisture, both the _____ methods were found to give results which are comparable to the LOD results. The analytical procedures and validation data for the LOD, KF, _____ methods are given in the NDA submission, Reference P-2, page 1 - 87, and are evaluated in this Review.

The immediate release tablet formulation contains ezetimibe and simvastatin active ingredients together with the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methylcellulose _____, citric acid monohydrate, butylated hydroxyanisole, propyl gallate, and magnesium stearate.

Formulation optimization studies were performed. The chosen tablet formulation was shown to give rapid in-vitro release of both active ingredients. The objective of the excipient selection process was to provide a physically and chemically stable formulation which was bioequivalent to the individual single entities when coadministered. The excipients used in the combination tablet formulation, with the exception of propyl gallate and hydroxypropyl methylcellulose, are excipients which are used in either the ezetimibe tablet or simvastatin tablet formulations. The active ingredients and excipients are all compatible with each other based on results from release testing as well as probe and formal stability studies.

There is no aseptic processing or sterilization needed for manufacture of the combination tablet. The excipient, lactose monohydrate, is in full compliance with the Guidance "The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-regulated Products for Human Use". According to the supplier, the lactose is derived from milk certified to originate from healthy animals and is collected in the same manner as milk fit for human consumption. In addition, the lactose is not prepared with the use of other ruminant materials.

2. Drug Substance

Ezetimibe drug substance is the same as used in the marketed product Zetia Tablets under NDA 21-445. It is a white powder that is freely soluble in organic solvents such as methanol and acetone and practically insoluble in water. Ezetimibe is hygroscopic above 45% RH. Ezetimibe is stable in the solid state.

Simvastatin drug substance is the same as used in the marketed product Zocor tablets under NDA 19766. It is a white to off-white powder that is freely soluble in chloroform, methanol and ethanol and relatively insoluble in water. Simvastatin is virtually non-hygroscopic. In the solid state, oxidation of simvastatin can occur, especially at elevated temperatures, therefore, _____ butylated hydroxyanisole is added to the drug substance

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

**Chemistry Assessment Section**

Ezetimibe is a cholesterol absorption inhibitor. Simvastatin is an HMG-CoA reductase inhibitor. Both active ingredients have been approved for the treatment of hypercholesterolemia.

The ezetimibe/simvastatin combination product contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Ezetimibe, as monotherapy, or administered with a statin, reduces elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia. Ezetimibe is also indicated as adjunctive therapy with a statin for homozygous familial hypercholesterolemia. Simvastatin is indicated to reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia.

In addition to its lipid-lowering effects, simvastatin is indicated to reduce the risk of mortality and cardiovascular morbidity in patients with or at high risk of coronary heart disease (CHD), regardless of lipid levels. The ezetimibe/simvastatin combination product is proposed as therapy for patients with primary hypercholesterolemia, including heterozygous familial hypercholesterolemia; mixed hyperlipidemia; or homozygous familial hypercholesterolemia.

C. Basis for Approvability or Not-Approval Recommendation

This NDA application can be Approved from a CMC perspective.

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Sharon Kelly, Ph.D. / June 15, 2004
Stephen Moore, Ph.D. /
Monika Johnson, Project Manager /

C. CC Block

**APPEARS THIS WAY
ON ORIGINAL**

(A)

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

104 pages

(A)

Chemistry Assessment Section

**B. Environmental Assessment Or Claim Of Categorical Exclusion
Claim of Categorical Exclusion Acceptable**

III List Of Deficiencies: None

**APPEARS THIS WAY
ON ORIGINAL**

Chemistry Assessment Section

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21687/000 Sponsor: MSP SINGAPORE
Org. Code : 510 NO CITY, , XX
Priority : 4S

Stamp Date : 24-SEP-2003 Brand Name : VYTORIN(EZETIMIBE/SIMVASTATIN)
20/40/80MG
FDUFA Date : 24-JUL-2004 Etab. Name:
Action Goal : Generic Name: EZETIMIBE/SIMVASTATIN
District Goal: 25-MAY-2004 COMBINATION TABLET
Dosage Form: (TABLET, ORALLY DISINTEGRATING)
Strength : 10, 20, 40, 80 MG

FDA Contacts: S. KELLY Review Chemist (HFD-510) 301-827-6394
S. MOORE Team Leader (HFD-510) 301-827-6401

Overall Recommendation: ACCEPTABLE on 14-JUL-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : 1012256 FEI : 1012256
MERCK AND CO INC
3517 RADIUM SPRINGS RD
ALBANY, GA 31708

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Chemistry Assessment Section

Establishment : CFN : 1036761 FEI : 1036761
MERCK AND CO INC
4633 MERCK RD
WILSON, NC 27893

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :
MERCK SHARP AND DOHME
21 TUAS SOUTH AVENUE 6
SINGAPORE, , SN

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-JUN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :
MERCK SHARP AND DOHME
VIA EMILIA 21
PAVIA, , IT 27100

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-JUN-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Chemistry Assessment Section

Establishment : CFN : 9613614 FEI : 3002807581
MERCK SHARP AND DOHME (AUSTRALIA) PTY LTD
SOUTH GRANVILLE, NEW SOUTH WALES, AS
DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 14-JUL-04
Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611927 FEI : 3002807653
MERCK SHARP AND DOHME DIV MERCK AND CO INC
SHOTTON LANE
CRAMLINGTON, , UK

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-MAY-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Chemistry Assessment Section

Establishment : CPN : 9610180 FBI : 3002807560
MERCK SHARP AND DOHME IRELAND LTD
TIPPERARY, CLONMEL COUNTY, EI
DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CPN : 9614153 FBI : 3002808083
SCHERING PLOUGH CORP
50 TUAS WEST DR
SINGAPORE, , SN 638408

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CPN : 2518332 FBI : 2518332
SHARP CORPORATION
23 CARLAND ROAD
CONSHOHOCKEN, PA 19428

DMP No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-03
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

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

/s/

Sharon Kelly
7/20/04 07:23:52 PM
CHEMIST

Stephen Moore
7/20/04 07:32:26 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

S. Edward Nevius
7/15/04 03:21:47 PM
BIOMETRICS

Submitted for Todd Sahlroot. Concur with review.

APPEARS THIS WAY
ON ORIGINAL