CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-445

CHEMISTRY REVIEW(S)

NDA/ANDA 21-445

Zetia

MSP Singapore Co., LLC

Chien-Hua Niu, Ph.D.
Division of Metabolics and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-445

2. REVIEW #: 2

3. REVIEW DATE: October 17, 2002

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original NDA Submission	December 27, 2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	7/24/02
Amendment	9/30/02
Amendment	10/3/02
Amendment	10/10/02

7. NAME & ADDRESS OF APPLICANT:

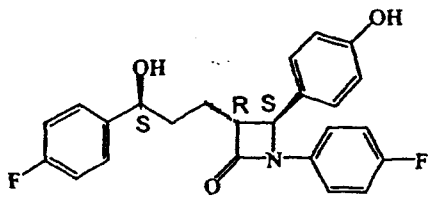
Name:	MSP Singapore Co., LLC
Address:	21 Thas South Avenue 6, Singapore 637766
Representative:	Joseph F. Lamendola, Ph.D., Schering Corporation
Telephone:	(908) 740-2628

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

Chemical Name:

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

Structural Formula:



Molecular Formula:

$C_{24}H_{21}F_2NO_3$

Molecular Weight:

409.4

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]		1	Adequate	27-Dec-96	[redacted]
[redacted]	III	[redacted]		1	Adequate	4-April-00	
[redacted]	III	[redacted]		1	Adequate	20-Sep-00	
[redacted]	III	[redacted]		1	Adequate	24-March-00	
[redacted]	III	[redacted]		1	Adequate	16-Feb-00	
[redacted]	III	[redacted]		1	Adequate	21-May-01	
[redacted]	III	[redacted]		1	Adequate	18-June-02	
[redacted]	III	[redacted]		1	Adequate	14-Sept-99	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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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)

APPEARS THIS WAY
ON ORIGINAL

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	—	Treatment of Hypercholesterolemia

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	**Acceptable**	10/7/02	Japob Choudhury
EES	**Pending**		Office of Compliance
Pharm/Tox	**Approval**	9/16/02	Indra Antonipillai
Biopharm	**Approval**	9/18/02	Wei Qiu
LNC	N/A		
Methods Validation	The method validation package will be sent to and validated by the FDA laboratories		
DMETS	Revision of the labels and labeling	10-MAY-2002	Marci Lee, PharmD
EA	Categorical exclusion		Chien-Hua Niu
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-445

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can be approved pending satisfactory cGMP inspection of facilities used to manufacture the drug substance.

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

II. Summary of Chemistry Assessments

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

ZETIA (ezetimibe) Tablet/10 mg is an immediate release product intended for the treatment of hyperchloesterolemia by selectively inhibiting the absorption of intestinal cholesterol.

DRUG SUBSTANCE: Ezetimibe, 1-(4-fluoropenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, is a new molecular entity manufactured by Schering-Plough LTD, Singapore Branch. The API has three chiral centers with the stereochemical configuration of [redacted] Ezetimibe (SCH 58235) was synthesized by [redacted]

The structure of ezetimibe was elucidated by a variety of analytical and [redacted] techniques, including [redacted] SCH 58235 is a white crystalline [redacted] powder with a melting point about 163°C [redacted] It has an aqueous solubility of about 0.01 mg/mL and a pKa of 9.75. SCH 58235 is freely soluble in organic media such as methanol and acetone.

[redacted] including the [redacted] of SCH 58235, have been observed. The [redacted] form is favored about [redacted] The drug substance is synthesized [redacted] Comparative solubility, rate of solution, intrinsic dissolution and stability of the [redacted] have been studied. The results have shown that the physical/chemical properties for the [redacted] are essentially identical, leading to the conclusion that any differences in [redacted] content of SCH 58235 will have no effect on bioavailability. Comparative stability studies on the [redacted] demonstrate that [redacted] forms have comparable stability. To further support this conclusion, [redacted] were studied in the formulated drug product. Tablets containing [redacted] have similar dissolution and stability characteristics as would be expected from the similarity of physical/chemical properties of the [redacted]

REVIEW NOTE

The particle size distribution of SCH 58235 was relatively tightly controlled. The results from the dissolution studies of the drug tablets show a trend to poorer dissolution for tablets prepared from drug substance batches with a median particle size much greater than When the tablet batches were prepared from the drug substance with lower median particle size the dissolution curves are essentially identical. Thus the small increase in the median particle size that may occur on storage of the drug substance has no significant effect on the product performance.

The proposed release specifications include molecular and configuration identity, moisture, specific rotation, assay, impurities, residual solvents, and particle size. The proposed regulatory methods have been validated. The impurity and degradation profiles have been investigated. Reference standards for API have been developed and characterized.

Based on data from ICH stability studies on 8 lots, SCH 58235 is stable for at least 24 months at room temperature when stored in

DRUG PRODUCT: The drug product is manufactured by Schering-Plough Products (Las Piedras, PR). The proposed commercial formulation for ezetimibe is a white to off-white capsule shaped, embossed, uncoated immediate release tablet. Each tablet contains 10 mg of ezetimibe combined with lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate and is manufacture via a employing Excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail. There is no provision for reprocessing.

The proposed release specifications included identification , moisture content content uniformity assay , degradation products , and dissolution. The proposed regulatory methods have been validated.

The tablets are packaged in two different packaging configurations (bottles and blisters). Bottles, 50 mL and 90 mL, are made of white HDPE resin and contain 30s (50 mL), 90s (50 mL0, and 500s (90 mL) tablets. Bottles are secured with either plastic child resistant closure screw cap (50 mL) or non-child resistant screw cap (90 mL). Both bottles contain cotton coiler.

The tablets (10 tablets) are also packaged in blisters. The blisters are sealed with a based

Based on data from ICH stability studies, ICH photostress conditions as well as WHO recommended storage conditions on three primary batches and two production-scale batches, the sponsor claims that the market product is stable for 24 months when stored at room temperature.

The sponsor has claimed a categorical exclusion from filling an environmental assessment under 21 CFR 25.31 (b).

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

The recommended dose of Zetia is 10 mg once daily. Zetia can be administered at any time of the day, with or without food.

REVIEW NOTE

C. Basis for Approvability or Not-Approval Recommendation

All outstanding CMC approvability issues have been addressed except the CGMP status. This application can be **approved** from CMC viewpoint pending the final recommendation by the Office of Compliance for the manufacturing sites for the drug substance. A number of comments and requests communicated to the applicant; however, these do not need to be resolved before the NDA can be approved

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./October 17, 2002
ChemistryTeamLeaderName/Date: Dr. Stephen Moore/
Project Manager Name/Date: Bill Koch

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Duu-Gong Wu

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ON ORIGINAL

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/s/

Chien-Hua Niu
10/21/02 04:04:48 PM
CHEMIST

Stephen Moore
10/21/02 04:29:55 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 21-445

Zetia

MSP Singapore Co., LLC

Chien-Hua Niu, Ph.D.
Division of Metabolics and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-445

2. REVIEW #: 1

3. REVIEW DATE: August 26, 2002

4. REVIEWER: Chien-Hua Niu, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	12/27/01

7. NAME & ADDRESS OF APPLICANT:

Name:	MSP Singapore Co., LLC
Address:	21 Thas South Avenue 6, Singapore 637766
Representative:	Joseph F. Lamendola, Ph.D., Schering Corporation
Telephone:	(908) 740-2628

Note: MSP Sigapore is a joint venture between Merck & Co and Schering Corporation.

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Zetia
b) Non-Proprietary Name (USAN): Ezetimibe
c) Code Name/# (ONDC only): SCH 58235
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: **1 S**

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: Lipid-Lowering Agent

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 10 mg/tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
_____SPOTS product – Form Completed

__X__Not a SPOTS product

APPEARS THIS WAY
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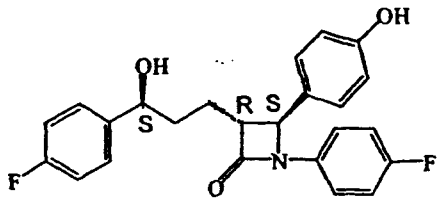
Chemical Name:

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

Structural Formula:



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DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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Biopharm	**Pending**		Wei Qiu
LNC	N/A		
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Microbiology	N/A		

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REVIEW NOTE

The Chemistry Review for NDA 21-445

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending (1) submission of additional CMC information described in List of Deficiencies; and (2) Satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

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

II. Summary of Chemistry Assessments

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

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The sponsor has claimed a categorical exclusion from filling an environmental assessment under 21 CFR 25.31 (b).

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

The recommended dose of Zetia is 10 mg once daily. Zetia can be administered at any time of the day, with or without food.

REVIEW NOTE

C. Basis for Approvability or Not-Approval Recommendation

This application is **approvable** from a CMC viewpoint. This recommendation is based upon several issues identified during the review. (1) General procedures for the synthesis of ezetimibe are outlined in the NDA submission. However, detailed information on each of the manufacturing processes is not provided and needs to be addressed. (2) Chemical structures of impurities and degradation products, including [redacted] compounds, are illustrated. However, information on how these [redacted] compounds are isolated/synthesized and how their structures are characterized needs to be provided. and (3) Regarding the manufacturing sites for the drug product, the final recommendation by the Office of Compliance is still pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Chien-Hua Niu, Ph.D./August 19, 2002
ChemistryTeamLeaderName/Date: Dr. Stephen Moore/
ProjectManagerName/Date: Bill Koch

C. CC Block

HFD-820: Dr. Eric Duffy/ Dr. Duu-Gong Wu

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

/s/

Chien-Hua Niu
9/17/02 09:18:54 AM
CHEMIST

Stephen Moore
9/17/02 02:28:06 PM
CHEMIST

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ON ORIGINAL