CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-445

CORRESPONDENCE

Office of Drug Safety

Memo

To: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-400

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: William C. Koch, R.Ph.
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

Date: August 22, 2002

Re: ODS Consult 01-0157-02; Zetia [Ezetimibe Tablets 10 mg]; NDA 21-445

This memorandum is in response to the August 8, 2002 request from your Division for a re-review of the proprietary name, Zetia. In our consult, dated April 8, 2002, DMETS did not recommend the use of the proprietary name "Zetia." We acknowledge the Division's decision to allow the sponsor to use the proprietary name "Zetia" despite DMETS' recommendation. The Division concluded that the names identified as potential look-alikes and sound-alikes do not pose a significant public health risk at this time. Our concerns as stated in the April 8, 2002, review are briefly summarized below.

> The primary concern was related to three sound-alike and/or look-alike drugs that already exist in the U.S. marketplace, namely, Cartia XT, Zebeta, and Zestril. Although a slight potential for confusion exists with Cartia XT, the risk is minimized due to the differing

strengths (10 mg vs. 120 mg, 180 mg, 240 mg, and 300 mg). DMETS feels that the potential for medication errors due to name confusion between Zetia and Zebeta or Zestril exists. This risk is increased due to the sound-alike (Zebeta) and look-alike (Zestril) similarities, in addition to the overlapping dosing interval (daily), strength (10 mg), and ordering physician population (cardiologists or general practitioners).

Since that review, the DMETS Expert Panel identified one additional name as having the potential to cause name confusion with Zetia. The Panel identified Zometa, a recently approved drug indicated for the treatment of hypercalcemia of malignancy, as a potential look-alike to Zetia. However, Zometa and Zetia differ in their formulation (injectable vs. tablet), recommended dose (4 mg vs. 10 mg), dosing interval (one time dose repeated in 7 days if needed vs. daily), and route of administration (intravenous infusion vs. oral). Based on these differences the potential for name confusion between Zetia and Zometa is minimal.

Although, we have not identified any additional concerns that would render the name unacceptable, DMETS has continuing concerns regarding the potential risk of medication errors with the use of the proprietary name Zetia. Based on these concerns, DMETS does not recommend the use of the proprietary name Zetia. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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

/s/

Denise Toyer
8/28/02 11:58:50 AM
PHARMACIST

Carol Holquist
8/28/02 01:02:27 PM
PHARMACIST

Jerry Phillips
8/28/02 01:36:41 PM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) HFD- 42 Attn: Karen Lechter			FROM: HFD-510	
DATE January 17, 2002	IND NO.	NDA NO. 21-445	TYPE OF DOCUMENT New Drug Application	DATE OF DOCUMENT November 19, 2001
NAME OF DRUG Zetia (ezetimibe) —— Tablets		PRIORITY Not Determined	CLASSIFICATION OF DRUG Not Determined	DESIRED COMPLETION DATE June 2, 2002

NAME OF FIRM Schering Corporation, Agent for MSP Singapore Company, LLC

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE-NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
MANUFACTURINGCHANGE/ADDITION	☐ CONTROL SUPPLEMENT	✗ OTHER *(SPECIFY BELOW)*
☐ MEETING PLANNED BY		Patient Package Insert Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND
DRUG USE e.g. POPULATION EXPOSURE,	SAFETY
ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached proposed patient package insert with Draft Package Insert

Jean Temeck, M. D. is the Medical Officer, (301) 827-0139.
William C. Koch, R.Ph., Regulatory Project Manager,(301) 827-6412.

SIGNATURE OF REQUESTER *{See appended electronic signature page}*	METHOD OF DELIVERY *(Check one)* MAIL X HANDX
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER *{See appended electronic signature page}*

Consult.088

{See appended electronic signature page}
Team Leader

Concurrence:_____

Mary H. Parks, M.D. Date
Deputy Director

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/s/

Mary Parks
1/17/02 01:03:59 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) HFD- 400 Attn: Sammie Beam			FROM: HFD-510	
DATE January 2, 2002	IND NO.	NDA NO. 21-445	TYPE OF DOCUMENT New Drug Application	DATE OF DOCUMENT November 19, 2001
NAME OF DRUG Zetia (ezetimibe) —— Tablets		PRIORITY Not Determined	CLASSIFICATION OF DRUG Not Determined	DESIRED COMPLETION DATE August 2, 2002

NAME OF FIRM Schering Corporation, Agent for MSP Singapore Company, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ✗ OTHER *(SPECIFY BELOW)*
  Trade Name Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached proposed trade name, Draft Package Insert and immediate container and carton labels.
William C. Koch, R.Ph., Regulatory Project Manager,(301) 827-6412.

SIGNATURE OF REQUESTER *{See appended electronic signature page}*	METHOD OF DELIVERY *(Check one)* MAIL X HANDX
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER *{See appended electronic signature page}*

Consult.088

{See appended electronic signature page}
Team Leader

Concurrence: _____

Mary H. Parks, M.D. Date
Deputy Director

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/s/

Mary Parks
1/3/02 09:40:08 AM

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ON ORIGINAL

IND: —

Drug: SCH 58235

Sponsor: Schering Corp.

Date submitted: April 11, 2002

Date received: April 12, 2002

Date reviewed: April 22, 2002

MEMO TO FILE

This is a 15-day safety report: second follow-up in a 56 year old female patient participating in study P00693 included in NDA 21445 which is under review.

Adverse events reported:

Study discontinuation due to elevation in liver transaminases and hemolytic anemia. Not clear if autoimmune or a drug-induced etiology. Patient subsequently died.

Regulatory Action:

1. Request hospital records and autopsy report.
2. Request submission of this report to the NDA
3. Forward information to Dr. Stadel who is reviewing the safety data submitted to the NDA for this drug.

Jean Temeck, M.D.

cc. HFD-510: Dr. Stadel and Mr. Koch

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/s/

Jean Temeck
4/22/02 11:07:11 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

DISCIPLINE REVIEW LETTER

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets, 10 mg.

Our review of the submitted patient package insert (PPI) is complete, and we have comments from the clinical review team. These comments are in the enclosure attached to this letter.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Enid M. Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

WITHHOLD 3 PAGE (S)

Draft

Labeling

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/s/

Enid Galliers
10/8/02 04:53:24 PM

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Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (Discipline Review)
COMIS Data Entry:	
Drafted by:	WCKoch10.07.02
Revised by:	EMGalliers10.08.02
Initialed by:	
Finalized:	WKoch.02
Filename:	C:\WINDOWS\Desktop\NDA21445\LTRdr100902.doc
DFS Key Words:	
Notes:	N000
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

DISCIPLINE REVIEW LETTER

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets, 10 mg.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have the following comments:

DRUG PRODUCT:

Regarding Labeling:

BLISTER CONTAINER LABEL (10s)

1. Clarify what information is intended at the bottom right in place of "XXXXXXXX".

2. Improve readability of the product name by modifying the use of the box surrounding the established name so that it does not run into the proprietary name above.

3. There is potential for destruction of the bar codes because they are placed along the perforation for the blister card. In the case of institutions that use bar code technology to document medication administration, a practitioner would not be able to scan a torn bar code. Consider relocating the bar code.

4. If possible, remove the [redacted] from the label to make room for increasing the prominence of the product name and dosage strength.

BLISTER CARTON LABELING

5. Consider relocating the tablet quantity information to the bottom portion of the carton, away from the dosage strength.

CONTAINER LABEL (30s, 90s, 500s)

6. Consider relocating the dosage strength information directly beneath the established name.

7. Please ensure that the tablet quantity is located away from the dosage strength to prevent confusion between the number of tablets in the container and the dosage strength information.

8. Remove [redacted] from the main focus area of the label.

9. Revise usual dosage statement to read, "One tablet daily. See insert."

10. Since the "30s and 90s" are unit-of-use size bottles, please assure that the packaging is child-resistant.

SAMPLE BLISTER CONTAINER LABEL (7s)

11. Remove or decrease the prominence of the word [redacted] so that the product name is the most prominent. Revise [redacted] to read [redacted]

12. Increase the prominence of the dosage strength.

13. Consider listing the LOT and EXP on the bottom portion of the label to increase the prominence of the product name.

SAMPLE BLISTER CARTON LABELING (7s)

14. Revise usual dosage statement to read, "One tablet daily. See insert."

15. Clarify what information is intended in place of "XXXXXXXX".

SAMPLE CONTAINER LABEL (30s)

16. See comments above.

17. Revise [redacted] to read [redacted].

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, for the
Division of Metabolic
and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Stephen Moore
10/3/02 04:05:23 PM

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Document Information Page

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Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (Discipline Review)
COMIS Data Entry:	
Drafted by:	WCKoch10.02.02
Revised by:	SKMoore10.02.02
Initialed by:	CNiu10.02.02/EMGalliers10.03.02
Finalized:	WKoch10.03.02
Filename:	C:\WINDOWS\Desktop\NDA21445\LTRdr100402.doc
DFS Key Words:	
Notes:	N000
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 3, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:

Attached is a copy of correspondence regarding NDA 21-445. The original document will arrive via US Mail.

Don't hesitate to call with any questions!

TO:	**FROM:**
Name: Deborah Urquhart, Ph.D.	Name: William C. Koch, R.Ph.
U.S. Regulatory Affairs	Regulatory Project Manager
Fax No.: (908) 740-6500	Fax No. 301-443-9282
Phone No.: (908) 740-2451	Phone No. 301-827-6412

Location: Schering Corporation, Agent for MSP Singapore Company, LLC

PAGES (including this cover sheet): Five (5)

M E SAGE CONFIRMATION

10/03/02 17:16
ID=DMEDP-CDER-FDA

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DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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BEST POSSIBLE COPY

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 3, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:
Attached is a copy of correspondence regarding NDA 21-445. The original document will arrive via US Mail.

Do not hesitate to call with any questions!

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

DISCIPLINE REVIEW LETTER

9/24/02

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets, 10 mg.

We also refer to your submission dated April 16, 2002.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

DRUG SUBSTANCE:

In addition, we provide the following comments/requests from the review team. These issues do not need to be resolved before the NDA can be approved:

DRUG SUBSTANCE:

WITHHOLD 1 PAGE (S)

DRUG PRODUCT:

Regarding Labeling:

(17) Please clarify what information is intended for "XXXXXXXX" in carton label, bottle label and blister package label.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

Stephen K. Moore, Ph.D.
Chemistry Team Leader I, for the
Division of Metabolic
and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Stephen Moore
9/24/02 02:42:31 PM

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: September 24, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:

Attached is a copy of correspondence regarding NDA 21-445. The original document will arrive via US Mail.

Don't hesitate to call with any questions!

TO:

Name: Ms. Bernadette Mauser
U.S. Regulatory Affairs
Fax No. (908) 740-5100
Phone No.: (908) 740-5576
Location: Schering Corporation

FROM:

Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No. 301-443-9282
Phone No. 301-827-6412

PAGES (including this cover sheet): Six (6)

Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (Discipline Review)
COMIS Data Entry:	
Drafted by:	WCKoch09.18.02
Revised by:	CNiu09.18.02/EGalliers09.18.02/SKMoore09.23.02
Initialed by:	
Finalized:	WKoch.02
Filename:	C:\WINDOWS\Desktop\NDA21445\LTR2dr092002.doc
DFS Key Words:	
Notes:	N000
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola, Ph.D.
Vice President, US Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ezetimibe) Tablets, 10 mg

We also refer to your November 19, 2001, submission to IND —— requesting a review of the proposed trademark Zetia.

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

The proposed proprietary name, Zetia, is not recommended.

The name Zetia has a sound-alike similarity to the previously approved drug Zebeta. Both names have the same beginning and ending sounds as well as the same number of syllables. Zetia and Zebeta have overlapping dosage strengths and dosing schedules. The risk for confusion is further increased because these products are used in a similar patient population. Zetia is used to treat patients with hypercholesterolemia, while Zebeta is used to treat hypertension. Both products will likely be prescribed by cardiologists and general family physicians. It is also likely that Zetia and Zebeta will be stored near each other in some pharmacies.

The Division, therefore, requests that a new proprietary name for this drug be submitted as an amendment to the application for review.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
7/8/02 07:56:35 PM

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Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Miscellaneous/General Correspondence Letters
Document Name:	General Advice Letter
Shortcut ID Code:	NDA-K0
COMIS Decision:	AD (ADVICE)
COMIS Data Entry:	
Drafted by:	wck/June 25, 2002
Revised by:	
Initialed by:	JTemeck07.02.02/MHParks07.02.02
Finalized:	WCKoch
Filename:	C:\WINDOWS\Desktop\NDA21445\LTRadv062702.doc
DFS Key Words:	
Notes:	11/19/01
Linking Instructions:	Link this outgoing letter to the incoming document that this letter concerns. If there is not a related incoming document, then link this outgoing letter to the initial submission of the NDA that this advice letter is being issued to.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: July 9, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:

Attached is a copy of correspondence
from the Division regarding NDA 21-445.
The official document will be sent by
U.S. Mail.

Don't hesitate to call with any questions.

TO:		**FROM:**	
Name:	Deborah Urquhart, Ph.D. U.S. Regulatory Affairs	Name:	William C. Koch, R.Ph. Regulatory Project Manager
Fax No.:	(908) 740-6500	Fax No.	301-443-9282
Phone No.:	(908) 740-2451	Phone No.	301-827-6412

Location: Schering Corporation, Agent for MSP Singapore Company, LLC

PAGES (including this cover sheet): Four (4)

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0362
CONNECTION TEL	919087406500
CONNECTION ID	SCHERING PLOUGH
ST. TIME	07/09 13:21
USAGE T	00'28
PGS. SENT	4
RESULT	OK

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: July 9, 2002

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Comments:

Attached is a copy of correspondence from the Division regarding NDA 21-445. The official document will be sent by U.S. Mail.

Don't hesitate to call with any questions.

TO:
Name: Deborah Urquhart, Ph.D.
U.S. Regulatory Affairs
Fax No.: (908) 740-6500
Phone No.: (908) 740-2451

FROM:
Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No. 301-443-9282
Phone No. 301-827-6412

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

INFORMATION REQUEST LETTER

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets.

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information requests from the Biometrics Reviewer. We request a prompt written response in order to continue our evaluation of your NDA.

As an extension of the May 23, 2002, discussion of our May 20, 2002, request for information, it seems that the validity of the Tarone method might be impaired by differences in mortality between trials. We have, therefore, the following requests:

1. Test for differences in mortality between trials among placebo rat groups.

2. If mortality is found comparable in Sprague Dawley rats, then in light of the power of such a study at 500 or more rodents per gender, include fatal tumors in Tarone analysis.

3. Test for differences in mortality between trials among placebo mouse groups.

4. If mortality is found comparable in ad libitum mice, 500 or more mice per gender, include fatal tumor in Tarone analysis of mice.

5. Tabulate or provide a separate electronic data table of the starting date of each rodent study, sorted by species.

Reference:

Thomas, D.G., N. Breslow, and J.J. Gart (1977), "Trend and Homogeneity Analyses of Proportions and Life Table Data," Computer and Biomedical Research, 10, 373-381.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
6/13/02 06:42:26 PM

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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: June 14, 2002

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Comments:

Attached is a copy of correspondence
from the Division regarding NDA 21-445.
The official document will be sent by
U.S. Mail.

Don't hesitate to call with any questions.

TO:		**FROM:**	
Name:	Deborah Urquhart, Ph.D. U.S. Regulatory Affairs	Name:	William C. Koch, R.Ph. Regulatory Project Manager
Fax No.:	(908) 740-6500	Fax No.	301-443-9282
Phone No.:	(908) 740-2451	Phone No.	301-827-6412

Location: Schering Corporation, Agent for MSP Singapore Company, LLC

PAGES (including this cover sheet): Four (4)

Document Information Page

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Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Information request letter for a pending NDA
Shortcut ID Code:	NDA-E1
COMIS Decision:	IR (INFORMATION REQUEST)
COMIS Data Entry:	
Drafted by:	wck/06.10.02
Revised by:	FHarrison06.12.02EGalliers06.13.02
Initialed by:	TSahlroot06.11.02/EGalliers06.12.02
Finalized:	WKoch.02
Filename:	C:\WINDOWS\Desktop\NDA21445\LTRirSTAT061402.doc
DFS Key Words:	
Notes:	N000
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

INFORMATION REQUEST LETTER

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets.

We are reviewing the Pharmacology/Toxicology section of your submission and have the following comments and information requests from the Biometrics Reviewer. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a new analysis of the rat data, electronically providing and using historical control data on the strain of rat used in study 96459 on dietary restriction. The approach of Tarone ("The Use of Historical Control Information in Testing for a Trend in Proportions", *Biometrics* **38**, 215-220, 1982) may be suitable.

> Include the historical control data in the usual SAS Transport format, and include the mean and range. The historical control data of [redacted] ("Spontaneous Neoplastic Lesions and Survival in Crl:CD(SD)BR Rats Maintained on Dietary Restriction", March 1998,) may be suitable.

2. Provide a new analysis of the mouse data, electronically providing and using historical control data on the strain of mouse used in study 96458, fed ad libitum.

3. Pool the two male rat placebo arms, redoing Figures 1(mean body weight) and 2(mean food consumption) and adding a figure for survival of male rats.

> Provide these graphs in a *.pdf file for inclusion in the review as a minor note on the differences in treatment arms.

We also have the following information request from the Pharmacology/Toxicology Reviewer:

1. Provide historical control data (range and mean) for diet restricted rats of this species (study # SN 96459).

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: May 21, 2002

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Comments:

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from the Division regarding NDA 21-445.
The official document will be sent by
U.S. Mail.

Don't hesitate to call with any questions.

TO:		**FROM:**	
Name:	Deborah Urquhart, Ph.D. U.S. Regulatory Affairs	Name:	William C. Koch, R.Ph. Regulatory Project Manager
Fax No.:	(908) 740-6500	Fax No.	301-443-9282
Phone No.:	(908) 740-2451	Phone No.	301-827-6412

Location: Schering Corporation

PAGES (including this cover sheet): Four (4)

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FOOD AND DRUG ADMINISTRATION
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5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: May 21, 2002

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Comments:

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Application #(s):	NDA 21-445
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Information request letter for a pending NDA
Shortcut ID Code:	NDA-E1
COMIS Decision:	IR (INFORMATION REQUEST)
COMIS Data Entry:	
Drafted by:	wck/05.14.02
Revised by:	KDavisBruno05.14.02&05.20.02/EGalliers05.17.02
Initialed by:	TSahlroot05.16.02
Finalized:	
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-445

INFORMATION REQUEST LETTER

Schering Corporation, Agent for
MSP Singapore Company, LLC
Attention: Joseph F. Lamendola
Vice President, U.S. Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Lamendola:

Please refer to your December 27, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zetia (ezetimibe) Tablets.

We are reviewing the Statistical section of your submission and have the following comments and information requests from the Statistical Reviewer. We request a prompt written response in order to continue our evaluation of your NDA.

The following preliminary requests for additional information are for studies P00474, P02173, P00680, P02243/P02257, and P01030. **If this information has already been submitted, please supply the location in the NDA.** Other things may be requested over the course of the review, as needed. Many of these may not be parts of protocol-mentioned primary analyses; rather, these may be used as "flagging" devices to see if further attention is needed. You may provide responses in installments. For a few topics, sample graphs or charts (HAM-D, MADRS, etc. were primary efficacy variables in those examples) were provided on August 31, 2001, by fax.

"Discussion and conclusion" is an essential part of your response. The words "smaller" and "greater" should be qualified by "numerically" or "statistically" (meaning statistically significant). Efficacy analyses are, generally, for the primary efficacy variables.

Please provide the responses and any further statistical submissions related to this NDA the same way as you have done for the NDA (hardcopy and electronic copy). Also, for immediate attention, desk copies to the statistical reviewer will be helpful.

1. For studies P00474, P02173 and P00680 only, please provide a graph and the corresponding Table for percent of patients continuing over time by treatment group (on the same page or graph), and corresponding tables and graphs for the percent of discontinuations due to adverse effects, when such dropouts are more than just a few.

2. Provide cumulative Distribution Functions (CDF) in Tables as well as graphs (all treatment groups on one graph) for the primary efficacy variable(s) at the primary time-point.

3.a. Investigate the effects of dropouts on OC and LOCF results. A few sample graphs for this purpose (dropout cohorts) were faxed before. However, additional graphs or methods, which you think throw better light on the issues, are always welcome.

3.b. Provide side-by-side comparisons (at each time point) of the means (or percents as relevant) of (1) observed cases and (2) unobserved cases using the last available observation for all treatment groups, for the primary efficacy measure and each actual (i.e. statistically significant) covariate.

4. Summarize results of your thorough investigation of confounding and interaction effects (but protocol-mentioned primary analysis remains the primary analysis), and also include covariation and interaction p-values. In each subgroup of the important factors, please provide treatment comparison p-values. [All of these for individual studies as well as for pooled data when some studies are poolable].

5.

6. For screening and exploratory purposes (not confirmatory), the reviewer would like to see (a) 2-sided p-values for all baseline comparisons (between treatment groups) corresponding to the efficacy comparisons, on baseline status, demographics, and other prognostic variables and (b) efficacy analyses by including in the model one at a time, two at a time, etc. of those factors/covariates for which the baseline pair-wise p-values were < .075. This is for individual studies as well as for pooled data depending on whether the imbalance occurred in the individual study or the pooled data.

Both the above should be done using original data and additionally with categorized data, if that is more meaningful.

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6. The following item seems to have been provided in some cases. Please provide, in addition to treatment by factor/covariate interaction p-values, side-by-side ninety-five percent confidence intervals (tables as well as graphs) for the difference between test drug and placebo (if no placebo, then for the intended comparisons), in change from baseline at different levels (2 or 3 except for centers) of a covariate (baseline variables, center, important time-point, concomitant diseases, concomitant medications, and other prognostic variables). This is only for the primary efficacy variable(s) at the primary time-point(s) unless the covariate under consideration is time.

Some ordering of these confidence intervals is desirable. For example, in the case of centers, first overall, then the largest center, then the next largest center, etc. The sample sizes should be mentioned below the X-axis. Where investigators or sites are combined for by-center 95% confidence intervals mentioned above, please present systematically individual investigator/site results which were qualitatively different to these combined results.

7. Present through efficient charts and plots, consistency or inconsistency of outcomes across various statistical methods, methods of handling missing data, studies, efficacy measures, etc., and discuss appropriateness or relevance of each (method, study, etc.). The reasons that could lead to the inconsistency should be investigated and stated, as far as possible.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
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FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: March 6, 2002

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Comments:

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Name:	Ms. Deborah Urquhart U.S. Regulatory Affairs	Name:	William C. Koch, R.P Regulatory Project Manager
Fax No.:	(908) 740-6500	Fax No.	301-443-9282
Phone No.:	(908) 740-2451	Phone No.	301-827-6412

Location: Schering Corporation

PAGES (including this cover sheet): Five (5)