

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-445

ADMINISTRATIVE DOCUMENTS

DOCUMENT INFORMATION PAGE

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COMIS Decision Code AP

Drafted by: WCKoch10.04.02

Revised by: MHParks10.22.02/WQiu10.23.02/LRipper10.24.02&10.25.02
/RJMeyer10.25.02

Initialed by: HAhn10.23.02/MHParks10.25.02/DGOrloff10.25.02

Finalized:

Filename: NDA21445/LTRap102702.doc

DFS Key Words:

Notes:

Version 12/13/2001

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

APPEARS THIS WAY
ON ORIGINAL

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

DATE: October 25, 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. 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): ()

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*** TX REPORT ***

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CONNECTION TEL		919087406500
CONNECTION ID	SCHERING PLOUGH	
ST. TIME	10/25 18:05	
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PGS. SENT	23	
RESULT	OK	

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

DATE: October 25, 2002

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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. 301-827-6410

NDA 21-445

Zetia (ezetimibe) Tablets, 10 mg

The preceding Action Letter has been reviewed by the undersigned:

Name	Discipline	Signature	Recommended Action	Date
J. Temeck, M.D.	Medical Officer Efficacy			
B. Stadel, M.D. MPH.	Medical Officer Safety			
M. Parks, M.D.	Deputy Director			
I. Antonipillai, Ph.D.	Pharm/Tox. Reviewer			
K. Davis-Bruno, Ph.D.	Supervisory Pharmacologist			
C. Niu, Ph.D.	Chemist			
S. Moore, Ph.D.	Chemistry Team Leader I			
W. Qiu, Ph.D.	Biopharmaceutics	/S/	AP	9/26/02
H. Ahn, Ph.D.	Biopharmaceutics Team Leader	/S/	AP	9/26/02
J. Choudhury, Ph.D.	Biometrics 2 Reviewer			
T. Sahlroot, Ph.D.	Biometrics 2 Team Leader			
E. Galliers	Chief, Project Mgt. Staff	/S/	—	9/24/02
D. G. Orloff, M.D.	Division Director	/S/		

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-445</u> / SE _____ - _____	
Drug <u>Zetia (ezetimibe, SCH58235) Tablets,</u> 10 mg	Applicant <u>MSP Singapore Company, LLC</u>
RPM <u>William C. Koch, R.Ph.</u>	Phone <u>(301) 827-6412</u>
<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Reference listed drug _____	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) <u>—</u>	
Application classifications: Chem Class <u>1</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>October 27, 2002</u> Secondary <u>October 27, 2002</u>

Arrange package in the following order:

Indicate N/A (not applicable),
X (completed), or add a
comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption

- ◆ Action Letter..... AP AE NA

- ◆ Labeling & Labels

FDA revised labeling and reviews.....	_____
Original proposed labeling (package insert, patient package insert)	X
Other labeling in class (most recent 3) or class labeling.....	N/A
Has DDMAC reviewed the labeling?	<input type="checkbox"/> Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels	X
Nomenclature review	X

- ◆ Application Integrity Policy (AIP): Applicant is NOT on the AIP.

Exception for review (Center Director's memo).....	_____
OC Clearance for approval.....	_____

- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) X Materials requested in AP letter

- ◆ Post-marketing Commitments N/A
 - Agency request for Phase 4 Commitments.....
 - Copy of Applicant's commitments

- ◆ Was Press Office notified of action (for approval action only)?..... Yes No
 - Copy of Press Release or Talk Paper.....

- ◆ Patent X
 - Information [505(b)(1)]
 - Patent Certification [505(b)(2)].....
 - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....

- ◆ Exclusivity Summary X

- ◆ Debarment Statement X

- ◆ Financial Disclosure
 - No disclosable information X
 - Disclosable information – indicate where review is located X

- ◆ Correspondence/Memoranda/Faxes X

- ◆ Minutes of Meetings X
 - Date of EOP2 Meeting October 4, 1999
 - Date of pre NDA Meeting April 25, 2001
 - Date of pre-AP Safety Conference September 23, 2002

- ◆ Advisory Committee Meeting N/A
 - Date of Meeting
 - Questions considered by the committee
 - Minutes or 48-hour alert or pertinent section of transcript

- ◆ Federal Register Notices, DESI documents N/A

CLINICAL INFORMATION:

- ◆ Summary memoranda (e.g., Office Director's memo, Division memo, Group Leader's memo) N/A (not applicable), ted), or add a

- ◆ Clinical review(s) and memoranda X

IN DRAFT

10/07/02

- ◆ Safety Update review(s) X
- ◆ Pediatric Information
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... X
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda X
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) N/A
 - Recommendation for scheduling _____
- ◆ Microbiology (efficacy) review(s) and memoranda N/A
- ◆ DSI Audits X
 - Clinical studies bioequivalence studies _____

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/A
- ◆ DMF review(s) N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption X
- ◆ Micro (validation of sterilization) review(s) and memoranda N/A
- ◆ Facilities Inspection (include EES report)
 - Date completed _____ Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda X
- ◆ Memo from DSI regarding GLP inspection (if any) N/A

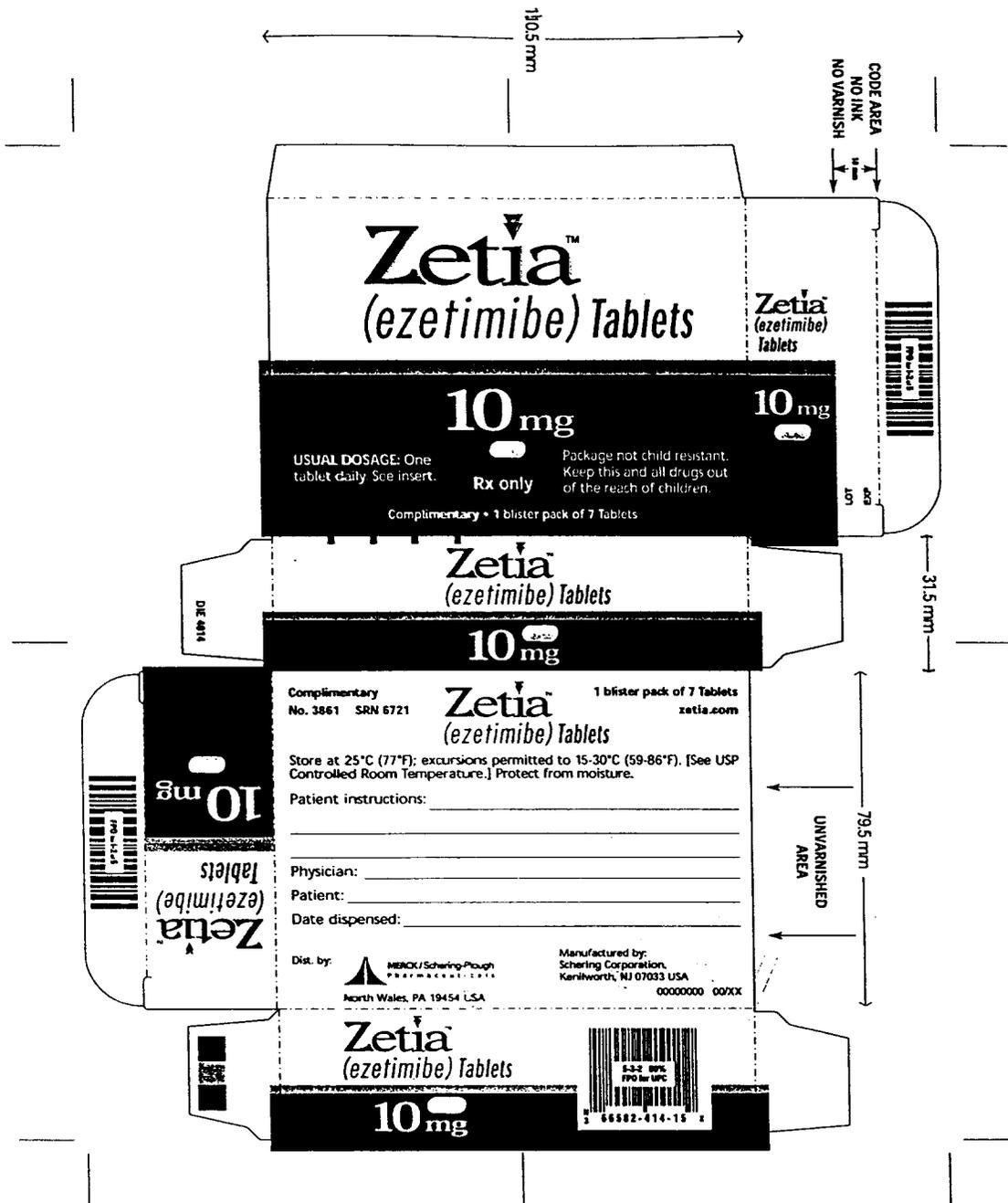
- ◆ Statistical review(s) of carcinogenicity studies X
- ◆ CAC/ECAC report X

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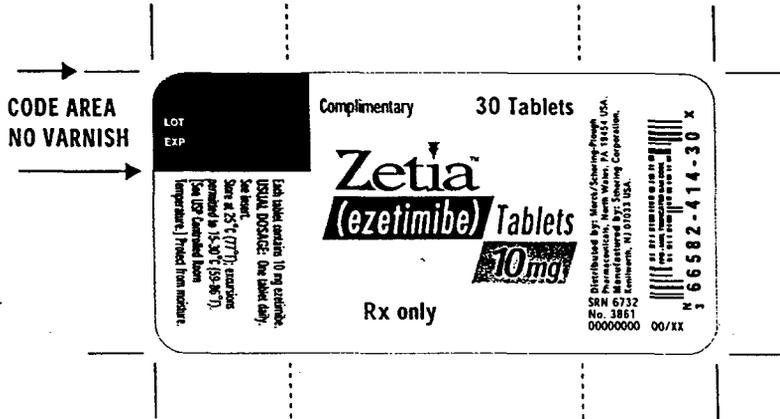
Labeling



TABLET IMAGE ART IS FPO

Industry
 OCT 14 2002

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CODE AREA
NO VARNISH

LABEL IS VARNISHED
PRIMARY PACKAGE IS CHILD-RESISTANT
TABLET IMAGE ART IS FPO

Industry
OCT 14 2002

APPEARS THIS WAY
ON ORIGINAL

CODE AREA
NO VARNISH

LOT
EXP

MDC 66582-414-31 30 Tablets

Zetia
(ezetimibe) Tablets
10mg

Rx only

Each tablet contains 10 mg ezetimibe.
USUAL DOSAGE: One tablet daily.
See insert.
Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
See USP Controlled Room Temperature. Protect from moisture.

Distributed by: Maco/Shering-Plough
Manufactured by: Maco/Shering-Plough
Kenilworth, NJ 07033 USA.

No. 3861
00000000 00/XX

66582-414-31 X

LABEL IS VARNISHED
PRIMARY PACKAGE IS CHILD-RESISTANT
TABLET IMAGE ART IS FPO

Industry
OCT 14 2002

APPEARS THIS WAY
ON ORIGINAL



LABEL IS VARNISHED
 PRIMARY PACKAGE IS CHILD-RESISTANT
 TABLET IMAGE ART IS FPO

Industry
 OCT 14 2002

APPEARS THIS WAY
 ON ORIGINAL

CODE AREA
NO VARNISH

LOT
EXP

MDC 66582-414-74 500 Tablets

Zetia
(ezetimibe) Tablets
10 mg

Rx only

Each tablet contains 10 mg ezetimibe.
NDA 020122.01. The tablet also contains
lactose monohydrate, croscarmellose sodium,
dibutyl sebacate, hydroxypropyl methylcellulose,
polyethylene glycol, and other inactive ingredients.
Store at 20° to 25° (68° to 77° F); excursions permitted to
15° to 30° (59° to 86° F). [See USP Controlled Room
Temperature.] Protect from moisture. This is a
white to off-white, oval tablet with a score line.
Keep out of reach of children. Exposure to
light does not affect the quality of the tablets.

Distributed by: Merck/Schering-Plough
Pharmaceuticals, Kenilworth, NJ 07033 USA
Manufactured by: Schering-Plough Corporation,
Kenilworth, NJ 07033 USA

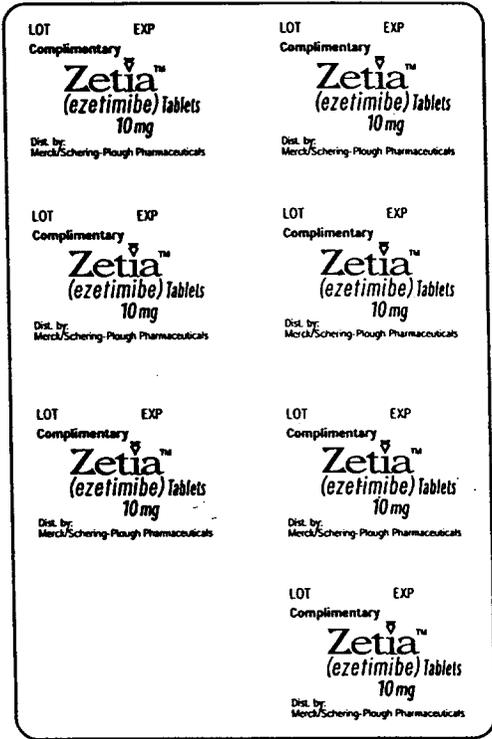
No. 3861
00000000 00/XX

66582-414-74 X

LABEL IS VARNISHED
TABLET IMAGE ART IS FPO

Industry
OCT 14 2002

APPEARS THIS WAY
ON ORIGINAL



Industry
OCT 14 2002

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Industry
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DRAFT

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		ODS POSTMARKETING SAFETY REVIEW	
TO: Julie Beitz, M.D., Director, Division of Drug Risk Evaluation, HFD 430		FROM: Jennie Chang, Pharm.D., Safety Evaluator, Office of Drug Safety, HFD-430	ODS PID # D020426
DRUG (Est): Ezetimibe	NDA/IND # 21-445	SPONSOR: _____	
DRUG NAME (Trade): Zetia		THERAPEUTIC CLASSIFICATION: Lipid-lowering	
EVENT: Pre-Approval Safety Conference			
Executive Summary: The purpose of this memo is to document information presented at the Pre-Approval Safety Conference (PSC) on September 23, 2002 for ezetimibe by ODS. Ezetimibe is a novel lipid-lowering agent that inhibits intestinal absorption of cholesterol and related phytosterols. Data was presented on the safety and efficacy of this drug by Jean Temeck, M.D., and Bruce Stadel, M.D., M.P.H., respectively. Recommendations by ODS to the package label were as follows: <ol style="list-style-type: none"> 1. Additional statement in the "Dosage and Administration" section of label to include the caution against the administration of _____ concomitantly with ezetimibe. 2. Placement of a similar bolded statement about _____ as noted in the "Warnings" section in the "Adverse Reactions" section. 3. Concern on the safety of simvastatin in conjunction with ezetimibe, especially at higher doses of simvastatin. <p style="text-align: center;">APPEARS THIS WAY ON ORIGINAL</p>			
Reviewer's Signature / Date: Jennie Chang, September 24, 2002		Team Leader's Signature / Date: Lanh Green, R.Ph., M.P.H., September 24, 2002	
cc: NDA #21-445 HFD-430 Beitz / Green / Chang / Brinker / La Grenade / Birdsong / Drug file			

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(ODS; HFD-400)

DATE RECEIVED: 1-3-2002	DUE DATE: 5-10-2002	ODS CONSULT #: 01-0157-1
--------------------------------	----------------------------	---------------------------------

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

THROUGH: William C. Koch, Project Manager
HFD-510

PRODUCT NAME:
Zetia
(Ezetimibe Tablets)
10 mg

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

NDA #: 21-445

SAFETY EVALUATOR: Marci Ann Lee, PharmD

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Zetia" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proprietary name "Zetia". DMETS recommends revising the labels and labeling as described in section III of this review.

**APPEARS THIS WAY
ON ORIGINAL**

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 8, 2002
NDA NUMBER: 21-445
NAME OF DRUG: Zetia (Ezetimibe Tablets) 10 mg
NDA SPONSOR: Schering Corporation, Agent for MSP Singapore Company, LLC

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products, for assessment of the proprietary name "Zetia", regarding potential name confusion with other proprietary or established drug names.

On November 20, 2001, the Division of Metabolic and Endocrine Drug Products received a letter from the sponsor indicating their wish to withdraw the proposed trademark candidate, — The new proposed name for ezetimibe is Zetia.

PRODUCT INFORMATION

Zetia is in a new class of lipid-lowering agents that selectively inhibit the intestinal absorption of cholesterol and related phytosterols. Zetia (ezetimibe) is used to treat primary hypercholesterolemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia. Zetia is administered alone or in combination with an HMG-CoA reductase inhibitor. The recommended dose for Zetia is 10 mg by mouth daily. Zetia can be administered any time of day, with or without food. The patient should be placed on a standard cholesterol-lowering diet before and during Zetia treatment. Zetia will be available as a 10 mg oral tablet.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{i, ii} as well as several FDA databasesⁱⁱⁱ for existing drug names that sound or look similar to Zetia to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis^{iv} Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies, to simulate the prescription ordering process.

ⁱ MICROMEDEX Healthcare Intranet Series, 102, MICROMEDEX, Inc., 610 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, PoisINDEX, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), INDEX Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 102).

ⁱⁱ Facts and Comparisons, 102, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-02, and online version of the FDA Orange Book.

^{iv} Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Zetia. Potential concerns regarding drug marketing and promotion related to each proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns with **Zetia** in regard to promotional claims.
2. The Expert Panel identified seven medication names that have potential for confusion with **Zetia**. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1. Potential sound-alike and look-alike names identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose	Look-alike or Sound-alike
Zetia	Ezetimibe Tablets 10 mg	10 mg by mouth daily	
Zebeta	Bisoprolol 5 mg, 10 mg oral tablets	5 to 10 mg by mouth once daily	Sound-alike
Zestril	Lisinopril 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg oral tablets	20 to 40 mg once daily	Look-alike
Cartia XT	Diltiazem 120 mg, 180 mg, 240 mg, 300 mg extended release capsules	180 to 240 mg once daily. Do not exceed 540 mg once daily.	Look-alike and Sound-alike
Zovia	Ethinyl estradiol and ethynodiol diacetate 1/35 and 1/50 21 and 28 day packs	One tablet once daily.	Look-alike and Sound-alike
Zerit	Stavudine 15 mg, 20 mg, 30 mg, 40 mg oral tablets 1 mg/mL powder for oral solution	30 mg to 40 mg every 12 hours	Look-alike
ReVia	Naltrexone 50 mg oral tablet	50 mg once daily	Look-alike and Sound-alike
Zetar	1 % whole coal tar over-the-counter (OTC) shampoo 30 % whole coal tar Rx only emulsion formulation	Rub shampoo into wet hair and scalp. Rinse and repeat as needed. Use once daily to at least twice a week.	Look-alike

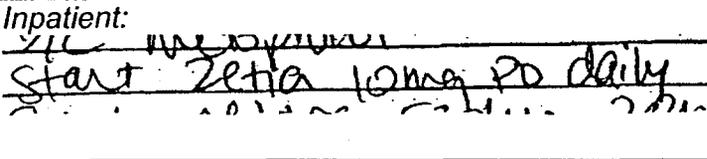
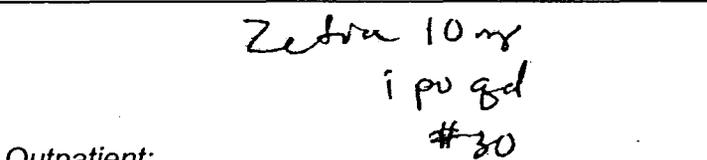
* Frequently used, not all inclusive

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology for Zetia studies

Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Zetia with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 114 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. DMETS staff members wrote inpatient and outpatient prescriptions for Zetia, each consisting of a combination of marketed and unapproved drug products. These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

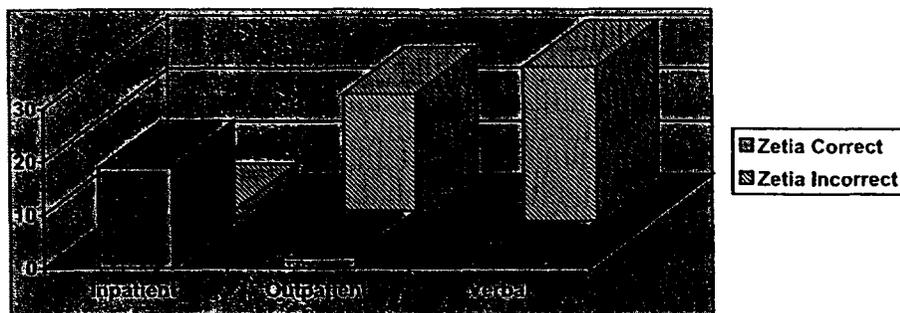
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ON ORIGINAL

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Zetia	
<i>Inpatient:</i> 	<i>Verbal:</i> Zetia 10 mg One tablet by mouth once daily. Dispense 30.
	
<i>Outpatient:</i>	

2. Results for Zetia studies

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Zetia" response	Other response
Written: Inpatient	39	21 (54%)	19 (90%)	2 (10%)
Written Outpatient	35	26 (74%)	2 (8%)	24 (92%)
Verbal:	40	29 (73%)	0 (0%)	29 (100%)
Total:	114	76 (67%)	21 (28%)	55 (72%)



Among the two written prescription studies, 26 of 47 (55 %) participants interpreted the name incorrectly. The most common misinterpretation was *Zetra*. Other incorrect responses included *Zastra*, *Zebra*, *Zestra*, *Zetin*, *Zetrin* and *Zofran*. *Zofran* is the proprietary name of a product currently marketed in the US.

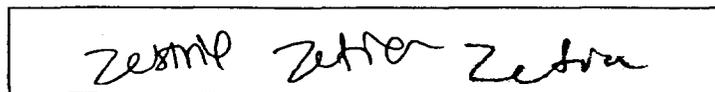
Among the verbal prescription study participants for Zetia, 29 of 29 (100 %) participants interpreted the name incorrectly. However many of the incorrect responses were phonetically equivalent to Zetia. These responses included *Zedia*, *Zedea* and *Zidia*. Other misinterpretations included *Aridia*, *Azedia*, *Expedia*, *Vedia* and *Zidiac*. Although none of the misinterpretations are marketed products in the US, there is a product called **Aredia** in the US, which is very similar to *Aridia*.

C. SAFETY EVALUATOR RISK ASSESSMENT

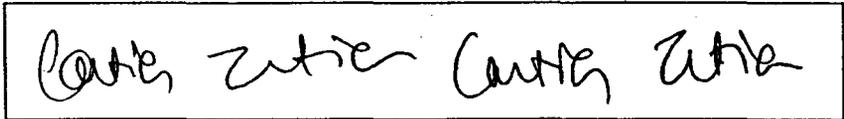
In reviewing the proprietary name, Zetia, the primary concerns raised by the expert panel were related to several proprietary names (see Table 1) that already exist in the US marketplace. We conducted prescription studies to simulate the prescription ordering process. There was no confirmation that Zetia could be confused with Zebeta, Zestril, Zetar, Zovia, Zerit, ReVia or Cartia XT. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

Zebeta and Zetia have sound-alike similarity. 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.

Zestril was identified by the expert panel to have potential for look-alike confusion with Zetia. In addition, while Zetia was not misinterpreted as Zestril in our written prescription simulation studies, two study participants noted that Zestril looked similar to Zetia. Although Zetia and Zestril have different indications, they are likely to be used in a similar patient population and prescribed by the same type of specialist as well as a general family physician. Both Zetia and Zestril are available as 10 mg oral tablet and administered once daily. Since the medications start with "Zet-" and "Zes-", it is likely that they will be stored near each other in some pharmacies.

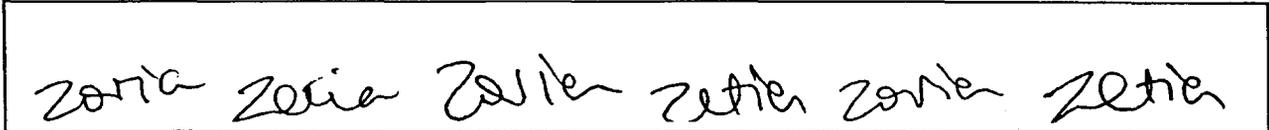


Cartia (actual name is Cartia XT) has potential for look-alike and sound-alike confusion with Zetia. Cartia XT is used to treat hypertension and Zetia will be used to treat patients with hypercholesterolemia. Cartia XT and Zetia are used to treat a similar patient population and will be prescribed by cardiologists as well as general family physicians. There are no overlapping dosage strengths, however both medications are administered once daily. All of these factors increase the likelihood for confusion between Cartia XT and Zetia.



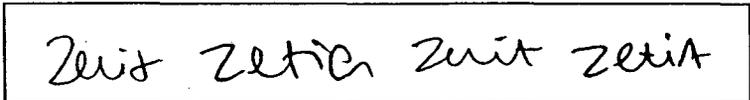
A rectangular box containing four handwritten words: 'Cartia', 'Zetia', 'Cartia', and 'Zetia'. The words are written in a cursive, handwritten style, with 'Cartia' and 'Zetia' appearing twice side-by-side to facilitate comparison.

Zovia has potential for look-alike and sound-alike confusion. The names share the same beginning and ending letters and the same number of letters and syllables, which contributes to their similarity. Despite this similarity, Zovia is a combination product that has a different indication, different dosage strengths, different packaging configuration and is typically used to treat a different patient population. All of these factors minimize the likelihood for confusion between these products.



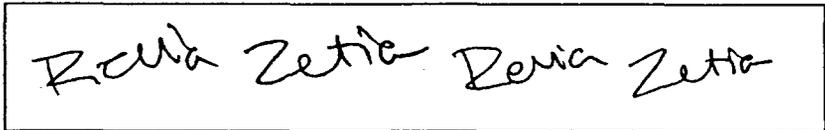
A rectangular box containing six handwritten words: 'Zovia', 'Zovia', 'Zetia', 'Zetia', 'Zovia', and 'Zetia'. The words are written in a cursive, handwritten style, with 'Zovia' and 'Zetia' each appearing twice side-by-side to facilitate comparison.

Zerit has potential for look-alike confusion with Zetia. Both names contain the same number of letters and start with "ZE-", which contributes to their look-alike similarity. However the risk for confusion is minimized because there is no overlap in their dosage strengths, dosing schedule, or indication. Zerit is typically prescribed by a specialist for patients with HIV infections. Zetia will be prescribed for an adult patient population by general family physicians.



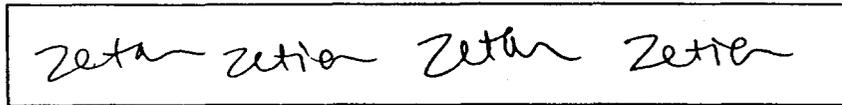
A rectangular box containing four handwritten words: 'Zerit', 'Zetia', 'Zerit', and 'Zetia'. The words are written in a cursive, handwritten style, with 'Zerit' and 'Zetia' appearing twice side-by-side to facilitate comparison.

ReVia has potential for look-alike and sound-alike confusion with Zetia. The letters "Z" and "R" can look similar when handwritten. The endings "-etia" and "-evia" can look and sound similar depending on how they are written and pronounced. These names share the same number of letters and syllables, which also contributes to their similarity. However the risk for confusion is minimized because ReVia is prescribed for a very specific patient population. ReVia is used to treat patients in detox programs and to treat patients with alcoholism. The risk for confusion is further decreased because there is no overlap in the dosage strengths available for these medications.



A rectangular box containing four handwritten words: 'ReVia', 'Zetia', 'ReVia', and 'Zetia'. The words are written in a cursive, handwritten style, with 'ReVia' and 'Zetia' appearing twice side-by-side to facilitate comparison.

Zetar and Zetia have potential for look-alike confusion. Both names begin with the letters "ZET-" however Zetar is available as an over-the-counter shampoo and with a prescription as 30% emulsion, unlike Zetia. Zetar has a different indication, different dosage formulations and different route of administration, minimizing the likelihood for confusion.

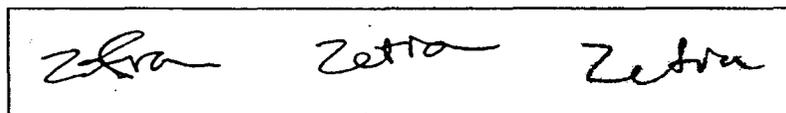


In addition to the medication names identified by the Expert Panel, our study participants identified two additional names that are similar to Zetia. These products are listed in Table 2, along with the dosage forms available and usual FDA-approved dosage.

Table 2. Potential sound-alike and look-alike names identified by Study Participants

Product Name	Dosage form(s) / Generic name	Usual adult dose	Look-alike or Sound-alike
Zetia	Exemilide Tablets 10 mg	10 mg by mouth daily	
Zofran	Ondansetron 4 mg, 8 mg, 24 mg oral tablets 4 mg/5 mL oral solution 2 mg/mL injection 32 mg/50 mL premixed injection (Also Zofran ODT as 4 mg and 8 mg orally disintegrating tablets)	8 mg twice daily (first dose 30 minutes before start of emetogenic chemotherapy; next dose 8 hours later; continue every 12 hours for 1 or 2 days after treatment) 8 mg 1 to 2 hours before each fraction of radiotherapy; 16 mg as a single dose 1 hour before induction of anesthesia; Various regimens depending upon indication.	Look-alike
Aredia	Pamidronate Disodium 30 mg and 90 mg Lyophilized powder for Injection	60-90 mg single IV infusion over 2 to 24 hours; 30 mg daily as a 4 hour infusion on 3 consecutive days; 90 mg as a 2 hour infusion every 3 to 4 weeks; various other regimens	Sound-alike

Zofran has potential for look-alike confusion with Zetia. One study participant indicated that the outpatient prescription was for Zofran. Zofran is used for a different indication, typically associated with a surgical procedure or course of emetogenic therapy. Zofran is available in dosage strengths that differ from Zetia and is administered on a different dosing schedule. The clinical characteristics and context of use for Zofran decrease the likelihood for confusion with Zetia.



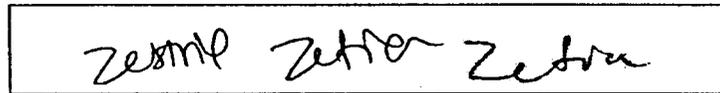
Aredia has potential for sound-alike confusion with Zetia. One study participant in the voice prescription study reported hearing "Aridia". Although there is no product with this name as the participant spelled it, there is a product available in the US market known as "Aredia". Aredia is used to treat patients with moderate to severe hypercalcemia associated with malignant neoplasms. The risk for confusion with Aredia and Zetia is minimized because there is no overlap in the indication, dosing, dosage formulation, route of administration, typical practice setting, or prescribing specialists.

III. COMMENTS TO BE PROVIDED TO THE SPONSOR

DMETS does not recommend use of the proprietary name, Zetia. See below for a description of some of the potential look-alike and sound-alike names that were identified.

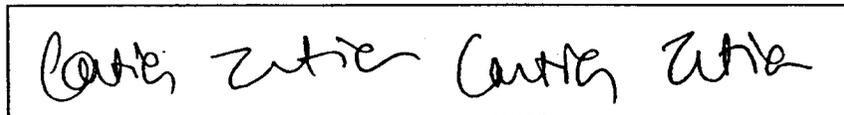
Zebeta and Zetia have sound-alike similarity. Both names have the same beginning and ending sounds as well as the same number of syllables. Zetia and Zebeta have overlapping dosage strengths and dosing schedules. The risk for confusion is further increased because these products are used in a similar 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.

Zestril was identified to have potential for look-alike confusion with Zetia. In addition, while Zetia was not misinterpreted as Zestril in our written prescription simulation studies, two study participants noted that Zestril looked similar to Zetia. Although Zetia and Zestril have different indications, they are likely to be used in a similar patient population and prescribed by the same type of specialist as well as a general family physician. Both Zetia and Zestril are available as 10 mg oral tablet and administered once daily. Since the medications start with "Zet-" and "Zes-", it is likely that they will be stored near each other in some pharmacies.



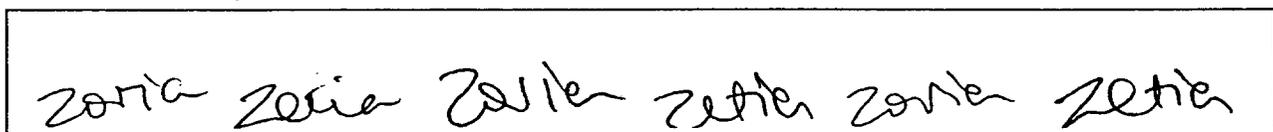
A rectangular box containing three handwritten words: "Zestril", "Zetter", and "Zebra".

Cartia (actual name is Cartia XT) has potential for look-alike and sound-alike confusion with Zetia. Cartia XT is used to treat hypertension and Zetia will be used to treat patients with hypercholesterolemia. Cartia XT and Zetia are used to treat a similar patient population and will be prescribed by cardiologists as well as general family physicians. There are no overlapping dosage strengths, however both medications are administered once daily. All of these factors increase the likelihood for confusion between Cartia XT and Zetia.



A rectangular box containing four handwritten words: "Cartia", "Zetia", "Cartia XT", and "Zetia XT".

Zovia has potential for look-alike and sound-alike confusion. The names share the same beginning and ending letters and the same number of letters and syllables, which contributes to their similarity. Despite this similarity, Zovia is a combination product that has a different indication, different dosage strengths, different packaging configuration and is typically used to treat a different patient population. All of these factors minimize the likelihood for confusion between these products.



A rectangular box containing six handwritten words: "Zovia", "Zovia XT", "Zetia", "Zetia XT", "Zovia XT", and "Zetia XT".

In the review of the container label, carton labeling, insert labeling and patient information leaflet for Zetia, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified areas of possible improvement, in the interest of minimizing potential user error.

A. BLISTER CONTAINER LABEL (10s)

1. Clarify what information is intended at the bottom right in place of "XXXXXXXX".
2. The established name should be revised to include the dosage formulation "tablet". (i.e., "Ezetimibe Tablet").
3. 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.
4. 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.
5. If possible, remove the _____ from the label to make room for increasing the prominence of the product name and dosage strength.

B. BLISTER CARTON LABELING

1. Consider relocating the tablet quantity information to the bottom portion of the carton, away from the dosage strength.
2. The established name should be revised to include the dosage formulation "tablets". (i.e., "Ezetimibe Tablets").

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

1. The established name should be revised to include the dosage formulation (i.e., "Ezetimibe Tablets").
2. Consider relocating the dosage strength information directly beneath the established name.
3. 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.
4. Remove _____ from the main focus area of the label.
5. Revise usual dosage statement to read, "One tablet daily. See insert."
6. Since the "30s and 90s" are unit-of-use size bottles, please assure that the packaging is child-resistant.

D. SAMPLE BLISTER CONTAINER LABEL (7s)

1. Remove or decrease the prominence of the word _____ ' so that the product name is the most prominent. Revise _____ to read _____
2. Increase the prominence of the dosage strength.
3. Consider listing the LOT and EXP on the bottom portion of the label to increase the prominence of the product name.

E. SAMPLE BLISTER CARTON LABELING (7s)

1. The established name should be revised to include the dosage formulation (i.e., "Ezetimibe Tablets").
2. Revise usual dosage statement to read, "One tablet daily. See insert."
3. Clarify what information is intended in place of "XXXXXXXX".

F. SAMPLE CONTAINER LABEL (30s)

1. See comments above.
2. Revise _____ to read _____

G. PATIENT INFORMATION LEAFLET

1. If possible increase the font size of the type for the patient information leaflet.
2. Remove _____ to prevent confusion in the section titled _____

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IV. RECOMMENDATIONS

- A. DMETS does not recommend the use of the proprietary name "Zetia".
- B. DMETS recommends the above labeling revisions that might lead to safer use of the product.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Marci Lee, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support (DMETS)

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this page is the manifestation of the electronic signature.**

/s/

Marci Ann Lee
5/10/02 03:02:05 PM
PHARMACIST

Carol Holquist
5/10/02 03:04:01 PM
PHARMACIST

Jerry Phillips
5/13/02 09:43:10 AM
DIRECTOR

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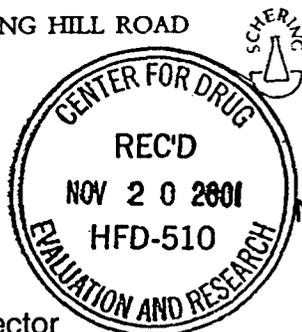
SCHERING CORPORATION

2000 GALLOPING HILL ROAD

KENILWORTH, N.J. 07033

N-2096c
ORIGINAL

TELEPHONE: (908) 298-4000



November 19, 2001

David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-510, Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

IND _____
SCH 58235 _____
Tablets Cholesterol Inhibitor
Serial No.: 209

SUBJECT: GENERAL CORRESPONDENCE: PROPOSAL FOR TRADEMARK

Dear Dr. Orloff,

Reference is made to our submission of June 5, 2001 requesting review by the Office of Post-Marketing Drug Risk Assessment (OPDRA) of _____ as a proposed trademark candidate for ezetimibe.

We wish to withdraw _____ as a candidate and request review of the following as the proposed trademark candidate for ezetimibe:

ZETIA

The data in our NDA (target 12/01) will support the following indication statements in the labeling:

TRADEMARK, administered alone or with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B _____ in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

TRADEMARK, administered with an HMG-CoA reductase inhibitor approved for homozygous familial hypercholesterolemia, is indicated for the reduction of elevated total-C and LDL-C levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

TRADEMARK is indicated as adjunctive therapy for the reduction of elevated sitosterol, _____ levels in patients with homozygous familial sitosterolemia.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,



Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

DU/jv

APPEARS THIS WAY
ON ORIGINAL

using ezetimibe to reduce plasma cholesterol levels in a mammal.

Patent Owner: Schering Corporation

1B. U.S. Patent No.: 5,846,966

Expiration Date: September 21, 2013

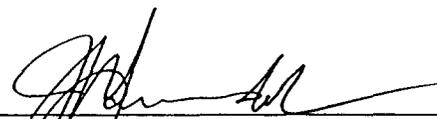
Type of Patent: Pharmaceutical compositions for reduction of plasma cholesterol levels containing ezetimibe in combination with an HMG CoA reductase inhibitor including, among others, simvastatin and methods of reducing plasma cholesterol levels by administering to a mammal ezetimibe in combination with a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors, including, among others, simvastatin

Patent Owner: Schering Corporation

The undersigned declares (a) that U.S. Patent No. 5,767,115 covers ezetimibe as the compound per se, pharmaceutical compositions containing ezetimibe and a method of using ezetimibe to reduce plasma cholesterol levels in a mammal; (b) that U.S. Patent No. 5,846,966 covers (i) pharmaceutical compositions containing ezetimibe for the reduction of plasma cholesterol levels in combination with an HMG CoA reductase inhibitor in a pharmaceutically acceptable carrier, and (ii) methods of reducing plasma cholesterol levels by administering to a mammal ezetimibe in combination with a cholesterol biosynthesis inhibitor selected from the group consisting of HMG CoA reductase inhibitors, including, among others, simvastatin; (c) that ezetimibe is the active ingredient in the tablet product used alone, or in combination with an HMG CoA reductase inhibitor, for the below-listed indications for which approval is being sought; and (d) that (i) the use of ezetimibe alone, or in combination with an HMG CoA reductase inhibitor, as adjunctive therapy

to diet, for the reduction of elevated total-C, LDL-C, Apo B, _____
_____ levels in patients with primary (heterozygous familial and non-
familial) hypercholesterolemia; (ii) the use of ezetimibe in combination with an HMG
CoA reductase inhibitor, approved for hypercholesterolemia, for the reduction of
elevated total-C and LDL-C levels in patients with homozygous familial
hypercholesterolemia, as an adjunct to other lipid-lowering treatments; and (iii) the
use of ezetimibe as adjunctive therapy for the reduction of elevated sitosterol. _____
_____ levels in patients with homozygous familial sitosterolemia are the
indications for which approval is being sought.

The undersigned further declares that (a) approval of the ezetimibe tablet
product for the above-listed indications is being sought under section 505 of the
Federal Food, Drug and Cosmetic Act, 21 USC § 355, and that (b) each of U.S.
Patent Nos. 5,767,115 and 5,846,966 claims ezetimibe, and a method using
ezetimibe, and a claim of patent infringement under one or both of U.S. Patent Nos.
5,767,115 and 5,846,966 could reasonably be asserted if a person not licensed by
the owner of each of the above-listed U.S. Patents engaged in the manufacture, use,
or sale of ezetimibe for use in the ezetimibe tablet product for the indications for
which approval is being sought.



Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs, SPRI
Agent for the MSP Singapore Co. LLC

1/30/02
Date

**APPEARS THIS WAY
ON ORIGINAL**

Exclusivity Checklist

NDA: 21-445				
Trade Name: Zetia Tablets, 10mg				
Generic Name: ezetimibe				
Applicant Name: MSP Singapore Company, LLC				
Division: HFD-510				
Project Manager: William C. Koch, R.Ph.				
Approval Date: October 25, 2002				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request? five				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	X
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

<p>2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.</p>					
<p>a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?</p>				Yes	No
<p>If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.</p>					
<p>Basis for conclusion:</p>					
<p>b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?</p>				Yes	No
<p>1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.</p>				Yes	No
<p>If yes, explain:</p>					
<p>2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?</p>				Yes	No
<p>If yes, explain:</p>					
<p>c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:</p>					
<p>Investigation #1, Study #:</p>					
<p>Investigation #2, Study #:</p>					
<p>Investigation #3, Study #:</p>					
<p>3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.</p>					
<p>a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")</p>					
<p>Investigation #1</p>				Yes	No
<p>Investigation #2</p>				Yes	No
<p>Investigation #3</p>				Yes	No
<p>If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:</p>					
<p>Investigation #1 -- NDA Number</p>					
<p>Investigation #2 -- NDA Number</p>					
<p>Investigation #3 -- NDA Number</p>					

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?			
Investigation #1	Yes	No	
Investigation #2	Yes	No	
Investigation #3	Yes	No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1			
Investigation #2			
Investigation #3			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.			
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?			
Investigation #1	Yes	No	
IND#:			
Explain:			
Investigation #2	Yes	No	
IND#:			
Explain:			
Investigation #3	Yes	No	
IND#:			
Explain:			

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/s/

Robert Meyer
10/31/02 02:17:01 PM

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Application #(s): NDA 21-445

Document Type: FORMS

COMIS Decision:

Drafted by: WKoch/09.17.02

Revised by:

Initialed by:

Finalized: WKoch/10.25.02

Filename: C:/Windows/Desktop/NDA21445/EXCLU102702.doc

DFS Key Words:

Notes: CC: M.HOLOVAC
T. Crescenzi

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Claim for Exclusivity (Section 20)

1. Pursuant to the provisions of Sections 505(c)(3)(D)(ii) and 505 (j)(5)(D)(ii) of the Food, Drug and Cosmetic Act (FDCA) and 21 CFR § 314.108(b)(2), the applicant claims five (5) years of exclusivity for its TRADEMARK (brand of ezetimibe) for the following indications: (i) the use of ezetimibe alone, or in combination with an HMG CoA reductase inhibitor, as adjunctive therapy to diet, for the reduction of elevated total-C, LDL-C, Apo B, _____ levels in patients with primary (heterozygous familial and non-familial) hypercholesterolemia; (ii) the use of ezetimibe in combination with an HMG CoA reductase inhibitor, approved for hypercholesterolemia, for the reduction of elevated total-C and LDL-C levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments; and (iii) the use of ezetimibe as adjunctive therapy for the reduction of elevated sitosterol, _____ levels in patients with homozygous familial sitosterolemia.

2. The applicant certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CFR § 314.108(a).

3. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a computer-assisted literature search that are relevant to the conditions for which the applicant is seeking approval is provided as **Attachment 1**.

4. The applicant certifies that it has thoroughly searched the scientific literature through a computer-assisted search of the Scholar database, and Dialog database encompassing the following subfiles: CHEMSEARCH, covering the period from January 1, 1990 to July 25, 2001; MEDLINE covering the period from January 1, 1990 to July 25, 2001; and EMBASE covering the period from January 1, 1990 to

July 25, 2001, for English and non-English literature relating to ezetimibe tablets in humans.

5. To the best of the applicant's knowledge, the list of scientific literature pertaining to ezetimibe tablets is complete and accurate, and in the opinion of the applicant, such published studies or publicly available information do not provide a sufficient basis for the approval of the use of ezetimibe tablets alone or in combination with a cholesterol inhibitor, including an HMG CoA reductase inhibitor, for the above-listed indications. The applicant's opinion that the studies or reports are insufficient is based on the following:

The literature does not contain adequate characterization of the efficacy and safety profile of ezetimibe tablets alone or in combination with a cholesterol inhibitor, including an HMG CoA reductase inhibitor, for the above-listed indications which is established by the data from the new clinical studies conducted by the applicant under IND, _____, and included in this application.

The applicant was the sponsor named in the Form FDA-1571 for IND _____ under which the new clinical trials were conducted.

**APPEARS THIS WAY
ON ORIGINAL**

16. DEBARMENT CERTIFICATION

The MSP Singapore Company, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.



Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs, SPRI
Agent for the MSP Singapore Co. LLC

1/30/02
Date

**APPEARS THIS WAY
ON ORIGINAL**

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
BLA-20
P.O. Box 4
West Point PA 19386-0004
Tel 484 344 2944
Fax 484 344 2515

December 27, 2001



David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products

Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Orloff:

NDA 21-445: ZETIA™ Tablets (Ezetimibe)

Original New Drug Application

Reference is made to the original New Drug Application (NDA) cited above for ZETIA™, submitted as an electronic archive on December 28, 2001 by MSP Singapore Co., LLP.

Reference is also made to an October 19, 2001 telephone conversation between Mr. William Koch of FDA and Dr. Deborah Urquhart of Schering-Plough Research Institute. This discussion involved the MSP Singapore Financial Disclosure information for NDA 21-445, in particular, the appropriate mechanism whereby Merck & Co., Inc. and Schering-Plough Research Institute could submit the financial disclosure information in a manner that would retain the confidentiality of the individual companies involved. Mr. Koch indicated that the Financial Disclosure information for both Merck and Schering-Plough would need to be submitted simultaneously with the NDA application. Additional reference is made to a December 5, 2001 email and subsequent December 7, 2001 telephone conversation between Dr. Urquhart (SPRI) and Dr. Linda Carter (FDA) during which Dr. Carter stated it acceptable for Merck to submit financial information in paper as described below and she would let the Division of Metabolic and Endocrine Drug Products know that the planned procedure was not a refuse-to-file issue.

Merck & Co., Inc. will provide MSP Singapore Co., LLP the Merck Financial Disclosure information in a sealed package marked confidential to be included with the submission of the original NDA 21-445. A copy of the cover letter will be supplied to Schering-Plough for inclusion in the NDA Administrative binder. Any questions the Division has with regard to the Merck Financial Disclosure information should be directed to Merck to maintain the confidentiality of the information. Merck Financial Disclosure information should not be disclosed to Schering-Plough Research Institute.

David Orloff, M.D., Director
NDA 21-445: ZETIA™ Tablets (Ezetimibe)
Page 2

With this submission, Merck is providing the Merck & Co., Inc. Financial Disclosure information for the original submission of NDA 21-445. All information is in an electronic format as indicated in the Table of Contents for this submission.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content; nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this submission should be directed to Robert E. Silverman, M.D., Ph.D. (484-344-2944) or, in my absence, to Bonnie J. Goldmann, M.D. (484-344-2383).

Sincerely,



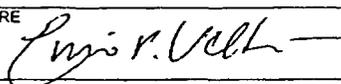
Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

Enclosure: CD

Hand Deliver

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**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service Food and Drug Administration	Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02						
CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS							
TO BE COMPLETED BY APPLICANT							
<p>With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).</p>							
Please mark the applicable checkbox.							
<p>(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).</p>							
Clinical Investigators	<table border="1" style="width: 100%; height: 60px;"> <tr><td style="width: 50%;"></td><td style="width: 50%;"></td></tr> <tr><td style="width: 50%;"></td><td style="width: 50%;"></td></tr> <tr><td style="width: 50%;"></td><td style="width: 50%;"></td></tr> </table>						
<p>(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).</p>							
<p>(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.</p>							
NAME Enrico P. Veltri, MD	TITLE Vice President, Clinical Research CV & Medical & Safety Service						
FIRM/ORGANIZATION Schering Plough Research Institute							
SIGNATURE 	DATE December 4, 2001						
Paperwork Reduction Act Statement							
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:	Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857						

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

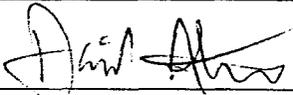
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David Arkowitz	Controller, MRL Financial Services
FIRM/ORGANIZATION	
Merck & Co., Inc.	
SIGNATURE	DATE
	November 21, 2001

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857