

# MESSAGE CONFIRMATION

03/06/02 16:07

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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:** Information request letter for a pending NDA  
**Shortcut ID Code:** NDA-E1

**COMIS Decision:** IR (INFORMATION REQUEST)

**COMIS Data Entry:**

**Drafted by:** wck/February 27, 2002  
**Revised by:** TSahlroot02.27.02&03.04.02  
**Initialed by:**  
**Finalized:**  
**Filename:** C:\WINDOWS\Desktop\NDA21445\LTRirSTAT030402.doc

**DFS Key Words:**

**Notes:** N000

**Linking Instructions:** Link this letter to the incoming document containing the information requiring further clarification.

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NDA 21-445

Schering Corporation, agent for  
MSP Singapore Co. LLC  
Attention: Joseph F. Lamendola, Ph.D.  
Vice President  
U.S. Regulatory Affairs  
2000 Galloping Hill Road  
Kenilworth, New Jersey 07033

Dear Dr. Lamendola:

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

We also refer to our acknowledgment letter dated January 25, 2002, which was sent prior to our determination of the drug review classification for this application.

We further refer to the February 6, 2002, telephone conversation Dr. David Orloff, Director of this Division, and Dr. Robert Silverman of your organization and yourself; during which the reasons for the Division's decision regarding this issue were discussed.

Our policy regarding determination of priority or standard review status is based on the proposed indications and alternative treatments marketed for the proposed indication. Upon careful consideration of your application, we have concluded that this application should receive a standard review. The user fee goal date is October 27, 2002.

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/

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Enid Galliers  
2/11/02 08:17:02 PM

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**Application #(s):** NDA 21-445

**Document Type:** NDA Letter

**Document Group:** NDA miscellaneous/ general Correspondence Letters

**Document Name:** Notification of Change NDA Review Priority

**Letter Code:** NDA-K4

**COMIS Decision:** No Decision Code

**Drafted by:** WKoch/02.01.02

**Revised by:** EGalliers02.11.02

**Initialed by:**

**Finalized:** WKoch02.11.02

**Filename:** C:/WINDOWS/DESKTOP/NDA21245/LTRfile021102.doc

**DFS Key Words:**

**Notes:** N000

**Linking Instructions:** Link the outgoing letter to the original N 000 incoming document for the NDA.

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Application #(s): NDA 21-445

Document Type: NDA Letter

Document Group: Acknowledgement Letters

Document Name: NDA Acknowledgement Letter

Letter Code: NDA-A1

COMIS Decision: No Decision Code  
(ACKNOWLEDGEMENT)

Drafted by: WKoch/January 16, 2002

Revised by: EGalliers01.22 & 24.02

Initialed by:

Finalized:

Filename: C:/WINDOWS/DESKTOP/NDA21245/LTRack012202.WPD

DFS Key Words:

Notes: N000

Linking Instructions: Link the outgoing letter to the original N 000 incoming document for the NDA.

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Meeting Date: October 21, 2002      Time: 12:30 PM      Location: PKLN Room #14B-45

NDA 21-445      Zetia (ezetimibe) Tablets

Type of Meeting:      Guidance Telephone Conference

External Participant:      Schering-Plough Corp.,

Meeting Chair:      Mary H. Parks, M.D., Deputy Division Director

External Participant Lead:      Michael Perelman, M.D., Regulatory Affairs,  
Schering Corp.

Meeting Recorder:      William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Mary H. Parks, M.D., Deputy Director  
Bruce V. Stadel, M.D., M.P.H., Clinical Reviewer  
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees (by phone) and titles:

Michael Perelman, M.D., Regulatory  
Affairs, Schering Corp.  
Deborah Urquhart, Ph.D., Manager, U.S.  
Regulatory Affairs

Meeting Objectives:

To discuss the significance of the fat soluble vitamin data in the applicant's study P00476.

Discussion:

The discussion centered around the clinical safety reviewer's three questions:

1. What is applicant's assessment of the significance of the fat soluble vitamin data?

The applicant reiterated its assessment which was submitted to the application in a letter dated October 1, 2002, which attributed the decreases in beta carotene and alpha tocopherol to the lipid lowering effects of ezetimibe and not to the drug itself. The decreases in the plasma particles that transport the fat soluble vitamins are decreased precipitating the observed decreases in the fat soluble vitamin levels.





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/s/

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Mary Parks  
10/25/02 02:39:47 PM

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**Document Information Page**

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Application #(s): NDA 21-445

Document Type: MEETING MINUTES

COMIS Decision:

Drafted by: WKoch/10.21.02

Revised by: BVStadel10.24.02

Initialed by: MHParks10.24.02

Finalized: WKoch/10.25.02

Filename: C:/Windows/Desktop/NDA21445/TCgide072302.doc

DFS Key Words:

Notes: 10.10.02

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**The MEETING MINUTES begin on the next page**

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<b>RECORD OF TELEPHONE CONVERSATION</b>	<b>DATE:</b> February 04, 2002 <b>Time:</b> 1330 hrs
<b>FDA Attendees:</b> William C. Koch, R.Ph., Regulatory Project Manager  <b>Objectives:</b> To discuss results of filing meeting held February 1, 2002.  <b>Discussion:</b> (1) The agent was informed that the NDA will be filed on February 25, 2002. (2) The agent was also informed that the review will be accomplished using the standard 10-month clock. The criteria for a priority review stated in MAPP 6020.3 were not met. The 10-month userfee goal date is October 27, 2002. (3) The "8-month" safety update should be submitted no earlier than July 27, 2002.  The agent projected that the 8-month safety update would be submitted in August 2002.  <b>Conclusion:</b> NDA 21-445 will be filed as a 10-month standard review.	<b>Telecon initiated by:</b> FDA  <b>NDA</b> 21-445  <b>Product name:</b> Zetia (ezetimibe) Tablets  <b>Firm name:</b> Schering Corporation, agent for MSP Singapore Co, LLC  <b>Name and title of person with whom conversation was held:</b> Ms. Deborah Urquhart U.S. Regulatory Affairs  <b>Telephone #:</b>  (908) 740-2451
{See appended electronic signature page}	
William C. Koch, R.Ph. _____ Regulatory Project Manager Date	

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/s/

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William Koch  
2/4/02 02:15:29 PM  
CSO

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Application #(s): NDA 21-445

Document Type: MEETING MINUTES

COMIS Decision:

Drafted by: WKoch/02.04.02

Revised by:

Initialed by:

Finalized: WKoch/ 02.04.02

Filename: C:/Windows/Desktop/NDA21445/TCfile020402.doc

DFS Key Words:

Notes:

Linking Instructions: N000

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FILING MEETING MINUTES

Meeting Date: February 01, 2002 Time: 09:30 AM Location: PKLN Room #15B-45

NDA 21-445 Zetia (ezetimibe) Tablets, 10 mg

APPLICANT: MSP Singapore Co., LLC

ATTENDEES:

David G. Orloff, M.D., Division Director, DMEDP  
Mary Parks, M.D., Deputy Division Director  
Jean Temeck, M.D., Clinical Reviewer (Efficacy)  
Bruce V. Stadel, M.D., M.P.H., Clinical Reviewer (Safety)  
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader  
Wei Qiu, Ph.D., Biopharmaceutics Reviewer  
Chien-Hua Niu, Ph.D., Chemistry Reviewer  
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2  
Japobrata Choudhury, Ph.D., Biometrics 2 Reviewer  
Karen Davis-Bruno, Ph.D., Supervisory Pharmacologist  
Kati Johnson, R.Ph., Chief, Project Management Staff  
William C. Koch, R.Ph., Regulatory Project Manager

BACKGROUND

Relevant IND: \_\_\_\_\_  
Priority Review Requested  
First member of class: \_\_\_\_\_

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Jean Temeck, M.D., Clinical (Efficacy) Bruce V. Stadel, M.D., M.P.H., Clinical (Safety)
Statistical:	Japobrata Choudhury, Ph.D., Biometrics 2
Pharmacology:	Indra Antonipillai, Ph.D., Pharmacology/Toxicology
Chemist:	Chien-Hua Niu, Ph.D., Chemistry Reviewer
Environmental Assessment (if needed):	Chien-Hua Niu, Ph.D., Chemistry Reviewer
Biopharmaceutical:	Wei Qiu, Ph.D., Biopharmaceutics
DSI:	Roy Blay, Ph.D., Senior Regulatory Review Officer

Project Manager: William C. Koch, R.Ph., RPM

Other Consults:  
ODS Trade Name Sammie Beam, Project Manager  
ODS PPI Karen Lechter, Analyst

Is the application affected by the application integrity policy (AIP) YES \_\_\_ NO X

Per reviewers, all parts in English, or English translation? YES X NO \_\_\_

CLINICAL – efficacy File X Refuse to file \_\_\_\_\_

Comments: Refer to ADVISORY COMMITTEE DISCUSSION Section.

CLINICAL - safety File X Refuse to file \_\_\_\_\_

Comments: Safety data available at filing is 6 to 12 weeks duration.

• Clinical site inspection needed: YES X NO \_\_\_\_\_

STATISTICAL – File X Refuse to file \_\_\_\_\_

Comments: Will discuss the three most crucial/pivotal protocols with the clinical efficacy reviewer for in-depth statistical review.

BIOPHARMACEUTICS – File X Refuse to file \_\_\_\_\_

Comments: Application includes only mass balance study and no relative BA study.  
We will be requesting dissolution profile with 3 lots (2 units per lot) including three conditions.

• Biopharm. inspection Needed: YES \_\_\_\_\_ NO X

PHARMACOLOGY – File X Refuse to file \_\_\_\_\_

CHEMISTRY – File X Refuse to file \_\_\_\_\_

Comments: None

• Establishment ready for inspection? YES X NO \_\_\_\_\_

PRIORITY/STANDARD REVIEW DISCUSSION:

ADVISORY COMMITTEE DISCUSSION:

Refer to POST-MEETING ACTIVITY Section.

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application, on its face, appears to be well organized and indexed. The application is suitable for filing.

The application is unsuitable for filing. Explain why:

REVIEW TIMELINES/REVIEW GOAL DATE (with labeling):

Final Draft Reviews to Team Leaders:	TBD
Final Reviews signed by Team Leader in DFS:	09/17/02
Action Package to Division Director:	09/27/02
Action Package to Office Director:	10/07/02

POST-MEETING ACTIVITY:

Since there are no major safety issues at this stage of the review, an Advisory Committee will not be requested.

*{See appended electronic signature page}*

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William C. Koch, R.Ph. Regulatory Project Manager  
HFD-510

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/s/

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William Koch  
6/10/02 03:07:13 PM

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Meeting Date: February 6, 2002      Time: 11:00 AM      Location: PKLN Room #14B-45

NDA 21-445      Zetia (ezetimibe) Tablets

Type of Meeting:      Guidance Telephone Conference

External Participant:      Schering Corporation, agent for  
MSP Singapore Co. LLC

Division Participant:      David G. Orloff, M.D., Director

External Participant Lead:      Joseph Lamendola, Ph.D., Regulatory Affairs

External participant Attendees (by phone) and titles:

Enrico Veltri, M.D., Clinical  
Joseph Lamendola, Ph.D., Regulatory Affairs  
Robert Silverman, M.D., Ph.D., Regulatory Affairs  
Penelope Giles, Ph.D., Regulatory Affairs

Meeting Objectives:

Discuss the sponsor's request for a priority review on this application.

Discussion Points:

1. For hereditary sitosterolemia:

I emphasized that the evidence of efficacy was based on an unvalidated surrogate. Although we were willing to accept sitosterol levels as an endpoint for approval of an indication to treat the disease, strictly speaking, the NDA contains no definitive evidence of ezetimibe as a significant therapeutic advance compared to existing therapy.

Furthermore, the study design, including the 4:1 randomization, as well as the small numbers of patients (by necessity for this very rare disease) was potentially flawed in permitting reliable estimates of the true treatment effect of the drug. Specifically, there were significant imbalances at baseline in several factors that appear to impact drug efficacy, including sitosterol and LDL-C levels.

Finally, an alternative study design may have negated some of these problems, such as a

[ ]

2. For homozygous familial hypercholesterolemia (hFH):

Again the evidence of efficacy is based on a surrogate, though we are quite comfortable with LDL-C lowering. Nonetheless, while clinical benefit is assumed, no data are presented. In addition, even if the study and the data are deemed to be adequate to support an indication in FH, ezetimibe is to be used as add-on therapy to a statin, both of which are adjunctive to apheresis or ileal bypass or other modalities. Since statins are used in hFH at the highest recommended doses, for obvious reasons, there is no evidence presented of dose sparing with avoidance of safety problems with ezetimibe added to a statin. Medical therapy already exists for hFH, as both simvastatin and atorvastatin are approved for the population.

Atorvastatin received a priority review because it was the first drug shown to lower to a clinically significant extent LDL-C in hFH. The simvastatin supplemental NDA for hFH was not reviewed as a priority. \_\_\_\_\_ that effected additional LDL-C lowering beyond the approved doses of simvastatin or atorvastatin would not receive priority designation unless there was clear evidence of clinical benefit over existing therapy, for example if it reduced CHD risk, or permitted less frequent apheresis, or in the completely unlikely event that it obviated altogether the need for apheresis. For all intents and purposes, while the rationale for the use of ezetimibe in hFH and indeed in run-of-the-mill hypercholesterolemia seems clear and readily acceptable, in hFH it may be considered, for purposes of review designation, as analogous to a higher dose of statin, which, as above, would not be reviewed as a priority unless certain specific evidentiary criteria were met.

Decisions (agreements) reached:

The sponsor expressed acceptance of this rationale.

Unresolved or issues requiring further discussion:

- None

Action Items:

I told the sponsor that we would send a letter stating that the NDA would get a standard review, but that we in the Division were as yet undecided as to how much detail would be included regarding our rationale for the decision.

Submitted by: *{See appended electronic signature page}*

\_\_\_\_\_  
David G. Orloff, M.D.  
Director

\_\_\_\_\_  
Date

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/s/  
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William Koch

2/12/02 10:20:16 AM

CSO

These minutes were reformatted/modified from an E-mail received from  
the signatory on February 7, 2002.

David Orloff

2/12/02 06:10:16 PM

MEDICAL OFFICER

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**Document Information Page**

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Application #(s): NDA 21-445

Document Type: MEETING MINUTES

COMIS Decision:

Drafted by: WKoch/02.08.02

Revised by: EGalliers02.11.02

Initialed by:

Finalized: WKoch/02.12 .02

Filename: C:/Windows/Desktop/NDA21445/TCdd020602.doc

DFS Key Words:

Notes:

Linking Instructions: N000

**END OF DOCUMENT INFORMATION 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: February 13, 2002

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**Comments:**

Attached are the Division minutes of the telephone conference with Dr. Orloff of February 6, 2002.

Please don't hesitate to call with any questions.

**TO:**

Name: Ms. Deborah Urquhart  
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

Location: Schering Corporation

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

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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
02/13 10:38	01'01"	908 298 6500	004/004	OK		0000

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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: February 13, 2002

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### Comments:

Attached are the Division minutes of the  
telephone conference with Dr. Orloff of  
February 6, 2002.

Please don't hesitate to call with any questions.



# **NO ADVISORY COMMITTEE MEETING**

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NO  
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or  
DESI DOCUMENTS  
REQUIRED

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## Memorandum

Date: 24 Oct. 2002

From: David E. Morse, Ph.D.  
Assoc. Director (Pharm./Tox.), Office of Drug Evaluation II

To: Robert Meyer, M.D.  
Director, Office of Drug Evaluation II

Cc: David G. Orloff, M.D., Dir., DMEP (HFD-510)  
Karen Davis-Bruno, Ph.D., Sup. Pharm./Tox., DMEDP (HFD-510)

Subject: NDA 21-445  
ZETIA® Tablets (ezetimibe)  
Review of Pharm./Tox. Information and Sections of Proposed Product Label

### I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-445, dated 12 Sept. 2002, I. Antonipillai, Ph.D.
2. Pharm./Tox. TL Memoranda, dated 10 Sept. and 26 Sept. 2002, K. Davis-Bruno, Ph.D.
3. Package Insert for ZETIA® Tablets, revision of 9 Oct. 2002
4. NDA 21-445 Action Package with Division Director Memo.
5. Related Product Labeling:
  - ADVICOR® Tablets
  - LESCHOL® Tablets and Capsules
  - LIPITOR® Tablets
  - MEVACOR® Tablets
  - PRAVACHOL® Tablets
  - ZOCOR® Tablets

### II. Background

The sponsor (MPS Singapore) is requesting approval of ZETIA® (ezetimibe) Tablets for use as chronic therapy (either as monotherapy or in combination with an HMG-CoA reductase inhibitor [statin]) for the reduction of elevated LDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial) in addition to reduction of elevated sitosterol/camosterol levels in patients with primary homozygous familial sitosterolemia.

Ezetimibe blocks the uptake of cholesterol in the intestinal wall by an as yet undefined mechanism. Ezetimibe has ACAT (acyl-coA cholesterol acyl transferase) inhibitory activity; which is an enzyme present in intestine and liver. In a rat liver microsome ACAT assay, ezetimibe had an  $IC_{50} = 18\mu M$  (7.4  $\mu g/ml$ ). Ezetimibe is extensively metabolized to a phenolic glucuronide in rats, the metabolite being equally or more potent than the parent compound in inhibiting cholesterol absorption from the gastrointestinal tract. There appears to be extensive first-pass metabolism to the glucuronide, with subsequent excretion in bile and retention within the GI tract (in association with the GI wall). The

glucuronide appears to be a less potent in ACAT inhibition than the unmetabolized structure. At least in the rat and hamster, the glucuronide can be hydrolyzed by intestinal glucuronidases back to the parent compound (it is not known whether this reaction occurs in humans). The therapeutic dose is recommended at 10 mg/day (AUC=0.7 µg h/ml).

### III. Comments and Conclusions

1. A review of the action package for NDA 21-445, ZETIA® Tablets (ezetimibe), indicates that the product has been adequately evaluated in multiple acute, sub-chronic and chronic repeat-dose toxicity studies (up to 6 months in rats and 1 yr in dogs), reproductive toxicity testing (Segment I-III in rats and Segment II in rabbits), genotoxicity and carcinogenicity testing (2 species) for approval for the chronic treatment (monotherapy) of primary hypercholesterolemia. In addition, combination repeat-dose toxicology studies of up to 3 months duration (rats and dogs), reproductive and genotoxicity studies support the approval of ezetimibe for chronic use in combination with any of the multiple previously approved 'statins' (HMG-CoA Reductase inhibitors) for the treatment of primary hypercholesterolemia.
2. A Review of the reproductive toxicity data for ezetimibe in rats, suggests that at doses up to 1000 mg/kg/day (~10X MRHD based on AUC) it did not affect fertility in males or females. Embryo fetal developmental studies (Segment II organogenesis studies) in rats given ezetimibe at doses up to 1000 mg/kg/day (~10X MRHD based on AUC) by oral gavage resulted in slightly increased incidences of fetal skeletal effects (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) in the absence of maternal toxicity. In rabbits (Segment II) given ezetimibe at doses up to 1000 mg/kg/day (~140 X MRHD based on AUC) an increased incidence of extra thoracic ribs in the absence of maternal toxicity was observed. Peri- and postnatal development was assessed in rats at oral gavage doses up to 1000 mg/kg/day (~10X MRHD based on AUC) without adverse findings. Ezetimibe has been shown to cross the placenta in rats and rabbits. Studies in rats have shown that as much as 50% of the maternal dose is excreted in the milk.

In female rats dosed with ezetimibe (up to 1000 mg/kg/day) combined with either pravastatin (125, 250, 500 mg/kg/day); simvastatin (5, 10, 25 mg/kg/day); atorvastatin (25, 50, 100 mg/kg/day) or lovastatin (10, 25, 50 mg/kg/day) during the period of organogenesis, resulted in no significant adverse drug effects at <10X human exposure based on AUC with a 10 mg/day therapeutic dose of simvastatin/atorvastatin or 20 mg/day pravastatin/lovastatin. (An exception is lovastatin where the NOAEL was <10X human therapeutic exposure.) Higher statin exposures (generally 10-100X MRHD based on AUC) resulted in fetal toxicity (weight decreases, blood vessel malformations and skeletal malformations (ribs, sternbrae) and/or variations (reduced/unossified bones) in the absence of maternal toxicity. Similarly, female rabbits dosed with ezetimibe (1000 mg/kg/day) combined with a 'statin' (pravastatin [5, 25, 50 mg/kg/day]; simvastatin [1, 5, 10 mg/kg/day]; atorvastatin [5, 25, 50 mg/kg/day] or lovastatin [2.5, 10, 25 mg/kg/day]) during organogenesis showed no significant drug induced adverse effects at ≤5X human exposure based on AUC with pravastatin and atorvastatin. NOAELs for simvastatin and lovastatin were <3X human therapeutic exposure. Higher exposures (generally >150X MRHD based on AUC except for lovastatin) resulted in fetal toxicity (skeletal malformations/variations and cardiac malformations) in the absence of maternal toxicity.

In combination studies with atorvastatin the toxicity profile was different consisting of an absent gall bladder and ectopic/misshapen kidneys in different fetuses.

Although the adverse reproductive effects of ezetimibe as monotherapy appear to be limited in scope, risks potentially associated with ezetimibe use in combination therapy appear to be more significant. It is recommended that these findings be described in the product label, but that they be clearly distinguished as being findings from monotherapy or combination treatment toxicology studies. It appears appropriate that specific direction and/or cross-reference to the 'statin' pregnancy labeling be included in the Pregnancy and Warning sections of the ZETIA® (ezetimibe) label.

4. A full review of the proposed product labeling has been deferred based on the expected 'APPROVABLE' action for this application.

General comments related to the product label follow:

- Under the heading of "Overdosage," it is suggested that the \_\_\_\_\_ of ezetimibe be included.

#### IV. Summary

A review of the action package for NDA 21-445, ZETIA® Tablets (ezetimibe), indicates that the product has been adequately evaluated in multiple acute through chronic repeat-dose toxicology studies (6-12 months in rats and dogs), full reproductive toxicity testing (Seg. I-III in rat and Seg. II in rabbit), genotoxicity and carcinogenicity testing for approval for chronic use in the treatment of hypercholesterolemia. Combination toxicology studies up to 3 months duration (2 species), genotoxicity and reproductive toxicity studies (multiple species) support product approval for chronic use in combination with HMG-CoA reductase inhibitors in the treatment of hypercholesterolemia.

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/s/

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David Morse  
10/25/02 04:58:14 PM  
PHARMACOLOGIST

**APPEARS THIS WAY  
ON ORIGINAL**

MEMORANDUM

Date: 9/26/02

From: Karen Davis-Bruno; Ph.D. Supervisory Pharmacologist HFD-510

To: NDA 21-445 Zetia (ezetimibe)

Re: Additional labeling comments

Based on a review of the Pharmacology/Toxicology Evaluation, Team Leader Memo 9/10/02 and sponsor's proposed labeling for NDA 21-445 further clarification is needed.

I recommend that Zetia for chronic monotherapy or in combination with an HMG-CoA reductase inhibitor (statin) for treatment of hyperlipidemia be approved. The basis of this recommendation is the extensive evaluation in acute, subchronic and chronic dose non-clinical toxicity studies (rat, dog), standard genotoxicity and reproductive toxicity standard test batteries, carcinogenicity studies (rat, mouse) and 3 month toxicity studies of Zetia in combination with statins (pravastatin, simvastatin, atorvastatin, lovastatin) in both rats and dogs in addition to combination genotoxicity and reprotoxicity test batteries with each of the above statins in combination with Zetia.

Non-clinical studies adequately support the safety of 10 mg/day ezetimibe monotherapy. Studies provided with ezetimibe in combination with various statins are adequate to assess safety of the proposed combination therapy. The Pharmacology/Toxicology Evaluation recommends approval of the monotherapy indication but states that the non-clinical studies do not support safety of ezetimibe in combination with statins since a NOAEL could not be established. Based on animal studies alone, the reviewer recommends that combination therapy should not be approved. However since clinical data from 3 month daily dosing with the combination do not show a safety concern, the reviewer defers to the Medical Officer's evaluation of safety. The Pharmacology/Toxicology Evaluation suggests that combination toxicity studies in rat and dog demonstrate an exacerbation of statin-associated toxicity profiles. Generally the target organs identified are identical to those identified with statin monotherapy (liver, muscle). The tissue toxicities are well characterized and clinically monitorable although they occur at lower exposures and dosing durations than with statin monotherapy. Novel toxicities have not been identified with combination therapy. The rat and dog combination therapy studies suggest that the enhanced statin toxicity is associated with a metabolic interaction in various species (rat, dog, rabbit). Increased levels of ezetimibe and statins are observed with combination therapy compared to exposures obtained with either agent alone at the same dose. Human pharmacokinetic combination therapy studies with various statins do not demonstrate this metabolic interaction and were considered adequately powered to detect this potential interaction if it existed according to the Biopharm evaluation. The metabolic interaction in rat has implications for combination reprotoxicity findings in the label.

The Pharmacology/Toxicology Evaluation recommends inclusion of the combination reprotoxicity findings in the label and calculates exposure multiples based on the statin component of the combination as this provides the most conservative determination of exposure. This approach is somewhat misleading since the rat clearly shows an increase in both ezetimibe and statin when given in combination. However this metabolic interaction is not observed in humans. The possibility exists that the threshold for statin toxicity might be lowered based on the animal studies although the clinical data do not support this, suggesting that the reprotoxicity findings with the combination therapy may be somewhat irrelevant to therapeutic use. The profile of rat and rabbit reprotoxicity findings are very similar to those reported for statin monotherapy although the findings occur at lower exposures. The concern for reproductive safety has been clearly indicated by the pregnancy category X designation for statins as a class. In my opinion the reprotoxicity findings for monotherapy should be included in the label and the combination therapy labeling should indicate the potential for a reduced threshold for statin related toxicity and refer to the individual statin pregnancy category X section of the individual label. The label should clearly indicate that ezetimibe monotherapy and in combination with statins is contraindicated during pregnancy. This suggestion differs from the Team Leader Memo of 9/10/02, which had suggested

In discussions with the Medical Team Leader, Pharm/Tox Associate Director

ODE II and ODE II Director this additional labeling was considered unnecessary for the reasons discussed above. The revised labeling recommendations are indicated below.

**Suggested Labeling:**

**Pregnancy Category C:**

There are no adequate and well controlled studies of ezetimibe in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

Oral gavage embryo-fetal developmental studies of ezetimibe have been conducted in rats and rabbits during \_\_\_\_\_ organogenesis. \_\_\_\_\_

\_\_\_\_\_ increased incidences of fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) at 1000 mg/kg/day (10 times the human exposure at 10 mg/day based on  $AUC_{0-24h}$  for total ezetimibe). In rabbits, \_\_\_\_\_

\_\_\_\_\_ increased the incidence of an extra pair of thoracic ribs at 1000 mg/kg/day (150 times the human exposure at 10 mg/day based on  $AUC_{0-24h}$  for total ezetimibe). Ezetimibe crosses the placenta when \_\_\_\_\_

Multiple dose studies of ezetimibe in combination with \_\_\_\_\_, HMG-CoA reductase inhibitors (statins) in rats and rabbits during organogenesis results in higher ezetimibe and statin exposures. \_\_\_\_\_

All HMG-CoA reductase inhibitors are contraindicated in pregnant and nursing women. When Zetia is administered with an HMG-CoA reductase inhibitor in women of child-bearing potential, refer to the pregnancy category and package labeling for the HMG-CoA reductase inhibitor.

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PHARMACOLOGIST

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## MEMORANDUM

Date: 9/10/02

From: Karen Davis-Bruno; Ph.D.; Supervisory Pharmacologist HFD-510

To: NDA 21-445

Zetia (ezetimibe)

Re: Review of the Pharmacology/Toxicology Evaluation & Sections of Proposed Product Label

Cc: Indra Antonipillai; Ph.D.

### BACKGROUND:

The sponsor (MPS Singapore a joint subsidiary of Merck and Schering-Plough) is seeking approval of Zetia (ezetimibe) for chronic monotherapy or in combination with an HMG-CoA reductase inhibitor (statin) for the reduction of elevated LDL-cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial) in addition to reduction of elevated sitosterol/camosterol levels in patients with primary homozygous familial sitosterolemia. The recommended therapeutic dose is 10 mg/day (AUC=0.7  $\mu\text{g h/ml}$ ).

Ezetimibe blocks cholesterol uptake in the intestinal wall by an unknown mechanism.

The therapeutic dose varies according to species ( $\text{ED}_{50}$ =0.5, 7, 30, 40, 700  $\mu\text{g/kg}$  in monkey, dog, rat, hamster, mice respectively) when animals were fed a high cholesterol diet. Animals in the toxicity studies were fed normal diets and therefore the cholesterol lowering effects were not seen. In humans 10 mg/day (167  $\mu\text{g/kg/day}$ ) lowers LDL-cholesterol by 18% and total cholesterol by 12-13%. Ezetimibe has ACAT (acyl-coA cholesterol acyl transferase) inhibitory activity; an enzyme present in intestine and liver. In the *in vitro* rat liver microsome ACAT assay, ezetimibe had an  $\text{IC}_{50}$ =18 $\mu\text{M}$  (7.4  $\mu\text{g/ml}$ ) which was ~3X lower than two known ACAT inhibitors (CL 2777082, PD 128042) simultaneously tested having  $\text{IC}_{50}$ = 5 and 6  $\mu\text{M}$  respectively.

[ Exposure levels have been achieved in rat and dog subchronic toxicity studies that are similar to the  $\text{IC}_{50}$  obtained in the *in vitro* rat ACAT assay and may explain the observed cardiac toxicity at exposures >10X human AUC. ]

Ezetimibe is extensively metabolized to a phenolic glucuronide (SCH 60663) and in rats this metabolite was found to be more potent (90%) than the parent (70%) in inhibiting cholesterol absorption. The glucuronide is less potent in ACAT inhibition than parent (8% at 50  $\mu\text{M}$  compared to 50% at 18  $\mu\text{M}$  with the parent). At least in the rat and hamster, the glucuronide can be hydrolyzed by intestinal glucuronidases back to the parent compound. In female rats 60% of  $^{14}\text{C}$ -drug undergoes enterohepatic recirculation and males only 30%. The majority of the radiolabeled drug was glucuronide conjugate (95%) in the pooled bile of rats given intraduodenal administration. This suggests that the potent inhibition of cholesterol absorption in the gut can be attributed to the extensive recirculation of the glucuronide.

In the 6 month dietary toxicity study in male rats given 1500 mg/kg/day ezetimibe (18X human AUC at 10 mg/day dose), target organ toxicity consists of minimal to mild bone marrow hyperplasia, ventricular myocardial degeneration/inflammation and moderate glomerular nephropathy (1/15 males). In high dose females given 500 mg/kg/day (18X human AUC at 10 mg/day) target organ toxicity consists of minimal to mild glomerular nephropathy and 1/15 females with ventricular degeneration. Although lower doses were not observed for histopathology the lack of appreciable findings suggest a NOAEL=750 mg/kg/day for males and 250 mg/kg/day for females which would provide at least a 10X exposure multiple based on AUC comparison.

In the 12 month dietary toxicity study in dogs, 300 mg/kg/day (10X exposure multiple based on AUC ) ezetimibe resulted in some minimal to mild lymph node inflammation. A 6 month dietary dog toxicity study revealed minimal myocardial mononuclear cellular infiltration in ¼ male dogs at 300 mg/kg/day. Interestingly, monotherapy in dogs treated chronically did not exhibit cardiac toxicity. The combination toxicity studies with statins similarly do not show a signal for cardiac toxicity.

One month dietary studies in rat and dog were performed to qualify impurities present at \_\_\_\_\_ in the clinical lots. Impurities were added by spiking the ezetimibe dose (exposures similar to previous dog, rat toxicity studies) with the various \_\_\_\_\_ impurities. The concentration of various impurities ranged from \_\_\_\_\_ of the dose. Low incidences of minimal severity in the heart and lymph nodes were identified target organs in rat and dog at 20X human, suggesting that the impurities in clinical lots did not produce any novel toxicity compared to ezetimibe alone.

Toxicity profiles in combination studies reflect exacerbated statin toxicity. However it is noteworthy that ezetimibe monotherapy did not show appreciable toxicity in subchronic studies despite dosing up to 1500 mg/kg/day in rat (17X human AUC) and 300 mg/kg/day (5X human AUC) in dog in studies up to 3 months. Target organ toxicity with monotherapy was only demonstrated with chronic dosing of ezetimibe. Rats exhibit increased exposure to atorvastatin and simvastatin in combination with ezetimibe and females had greater exposure than males. This may reflect the increased rate of enterohepatic recycling in females (60%) compared to males (29%). However with pravastatin there doesn't seem to be an increase in exposure in rat. In dogs combination studies with lovastatin and simvastatin show increased exposure but not with atorvastatin or pravastatin. The toxicity profile in dog may reflect the increased sensitivity of this species as previously seen with statin monotherapy. The absence of appreciable ezetimibe target organ toxicity in the combination studies combined with the toxicity profile observed (hepatotoxicity) suggests that the toxicity seen is attributable to the statin. Novel toxicities have not been observed in the combination 3 month studies. The statin toxicity profile has been well established and is clinically monitorable. Generally clinical data with statins has been less concerning than animal findings presumably due to species differences in metabolism and species differences in sensitivity (dog).

Ezetimibe alone or in combination with statins was not mutagenic/cytogenetic in the bacterial mutagenicity (Ames) test, *in vitro* chromosome aberration assay in human

lymphocytes and *in vivo* mouse micronucleus test. Ezetimibe spiked with clinical lot impurities was not mutagenic/cytogenetic in the Ames or *in vivo* mouse micronucleus.

Ezetimibe was given in the diet for two years in carcinogenicity studies in rats and mice. These studies were reviewed by ECAC on 4/16/02 and were considered adequate studies which did not reveal any significant carcinogenic potential for ezetimibe.

In oral gavage fertility studies in rats doses of ezetimibe up to 1000 mg/kg/day (~10X human exposure at 10 mg/day based on AUC both genders) did not affect fertility. Embryo fetal developmental studies (Segment II) in rats given ezetimibe at doses up to 1000 mg/kg/day (~10X human exposure at 10 mg/day based on AUC) by oral gavage resulted in increased incidence of fetal skeletal effects (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) in the absence of maternal toxicity.

In oral gavage Segment II studies in rabbits given ezetimibe at doses up to 1000 mg/kg/day (140 X human exposure at 10 mg based on AUC) increased incidence of extra thoracic ribs in the absence of maternal toxicity was observed. Ezetimibe has been shown to cross the placenta in rats and rabbits. Studies in rats have shown that as much as 50% of the maternal dose is excreted in the milk. Postnatal development was assessed in rats at oral gavage doses up to 1000 mg/kg/day without any relevant findings. One F1 female died day 155 given 100 mg/kg/day however higher doses in this study or in the Segment II assessment did not demonstrate mortality.

In female rats given oral gavage doses of ezetimibe (1000 mg/kg/day) combined with either pravastatin (125, 250, 500 mg/kg/day); simvastatin (5, 10, 25 mg/kg/day); atorvastatin (25, 50, 100 mg/kg/day) or lovastatin (10, 25, 50 mg/kg/day) during organogenesis resulted in an absence of significant drug-induced changes at <10X human exposure based on AUC with a 10 mg/day therapeutic dose of simvastatin/atorvastatin or 20 mg/day pravastatin/lovastatin. An exception is lovastatin where the NOAEL was <10X human therapeutic exposure. Higher statin exposures (generally 10-100X human therapeutic exposure based on AUC) resulted in fetal toxicity (weight decreases, blood vessel malformations and skeletal malformations (ribs, sternbrae) and/or variations (reduced/unossified bones) in the absence of maternal toxicity.

In female rabbits given oral gavage doses of ezetimibe (1000 mg/kg/day) combined with either pravastatin (5, 25, 50 mg/kg/day); simvastatin (1, 5, 10 mg/kg/day); atorvastatin (5, 25, 50 mg/kg/day) or lovastatin (2.5, 10, 25 mg/kg/day) during organogenesis resulted in an absence of significant drug induced changes at ≤5X human exposure based on AUC with pravastatin and atorvastatin at a therapeutic dose. Simvastatin and lovastatin had NOAELs that were <3X human therapeutic exposure. Higher exposures (generally >150X human therapeutic exposure based on AUC except for lovastatin) resulted in fetal toxicity (skeletal malformations/variations and cardiac malformations) in the absence of maternal toxicity. In combination studies with atorvastatin the toxicity profile was different consisting of an absent gall bladder and ectopic/misshapen kidneys in different fetuses.

RAT	NOAEL (mg/kg/d)	Exposure Multiple (AUC)*	Toxicity	Toxic Dose (mg/kg/d)	Exposure Multiple*
Ezetimibe (1000 mg/kg/d) +					
Pravastatin	250	16X	↓ dam wt. ↓ skeletal ossification	500	
Simvastatin	10	7X	↓ fetal wt., blood vessel malformations skeletal variation/malformation	25	12X
Atorvastatin	50	30X	↓ dam/fetal wt. ↓ ossification sternebrae	100	103X
Lovastatin	<10	?	Skeletal variation/malformation Unossified sternebrae fused ribs, focal thickening of ribs	10	?

RABBIT	NOAEL (mg/kg/d)	Exposure Multiple (AUC)*	Toxicity	Toxic Dose (mg/kg/d)	Exposure Multiple*
Ezetimibe (1000 mg/kg/d) +					
Pravastatin	5	200X	Tail malformations & fused caudal vertebrae	25	210X
Simvastatin	1	150X	Cardiac malformations Tail/vertebral malformations	5	163X
Atorvastatin	5	200X	Gall bladder absent Ectopic/misshapen kidney	25	206X
Lovastatin	<2.5	?	Maternal tox Skeletal variations		?

TK evaluations were not performed in pregnant animals in the lovastatin combination Seg. II studies.

\* exposure multiple based on ezetimibe AUC

**COMMENTS/CONCLUSIONS:**

A review of the Pharmacology/Toxicology Evaluation for NDA 21-445, Zetia (ezetimibe), indicates that the product has been extensively evaluated in acute, sub-chronic and chronic repeat dose non-clinical toxicity studies (including 6 and 12 month multiple dose toxicity in rat and dog respectively), standard batteries of genotoxicity and reproductive toxicity studies and carcinogenicity evaluations in rat and mouse to support potential approval for chronic use in the treatment of hyperlipidemia. In addition the sponsor has provided 3 month toxicity studies of ezetimibe in combination with various statins (pravastatin, simvastatin, atorvastatin, lovastatin) in both rat and dogs in support of the proposed combination indication, along with combination genotoxicity and reprotoxicity test batteries.

Review and revision of the proposed product label: Refer to Dr. Antonipillai's labeling review with the following comments:

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**RECOMMENDATION: AP**

Nonclinical studies adequately support the safety of the 10 mg/day ezetimibe monotherapy. The studies provided with ezetimibe in combination with pravastatin, simvastatin, atorvastatin and lovastatin are adequate to assess safety of the indication for combination therapy. However these combination toxicity studies in rat and dog suggest synergistic statin-associated toxicity profiles. The target organ toxicities are that of statins, but occur at lower doses and shorter durations of treatment. These synergistic statin toxicities are well known and consist of liver and muscle degeneration which are monitorable. Novel toxicity has not been demonstrated with ezetimibe in combination with various statins. The animal studies suggest that this synergistic toxicity is associated with a metabolic interaction in rat and may relate to the enhanced sensitivity of the dog to statin toxicity. Human pharmacokinetic studies (2 week duration) do not exhibit this metabolic interaction. Safety evaluation of the clinical trials (3 month duration) do not show an enhanced potential for statin toxicity suggesting a limited potential for clinical safety concern. Therefore **Pharmacology/Toxicology recommends approval of this application pending the labeling changes indicated.**

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PHARMACOLOGIST

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NDA 21-445

Signed into DFS on 2/28/02

**45 Day Meeting Checklist  
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

**NDA 21-445:** This NDA is a 505(b)(1) application.

**Submission date:** 12/27/2001

**Sponsor:** MSP singapore Co., LLC, Singapore (Joint venture by Merck and Schering Co.)

**Drug:** Ezetimibe (Zeita)

**Introduction:** Ezetimibe (Zeita) is a lipid lowering drug, which blocks the intestinal absorption of cholesterol. The indication is to lower cholesterol with the drug alone or in combination with statins in hypercholesterolemia patients. Also it is indicated for patients with homozygous familial hypercholesterolemia and for homozygous sitosterolemia patients.

ITEM: NDA 21-445	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		<b>APPEARS THIS WAY ON ORIGINAL</b>
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		

NDA 21-445

<p>4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)</p>	<p>Yes</p>		<p>Have electronic files of the carcinogenicity studies been submitted for statistical review? Yes</p>
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ITEM	YES	NO	COMMENT
<p>5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?</p>	<p>Yes</p>		<p>The 3-month toxicity/TK studies of ezetimibe in combination with certain statins were conducted to look at the combined toxicity of two drugs in rats/dogs</p>
<p>6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?</p>	<p>Yes</p>		<p>1. The drug substance contains <u>                    </u> impurities. sponsor has conducted two dietary toxicity studies of 28-29 days duration in rats and dogs with the <u>                    </u> impurities of ezetimibe. These impurities are</p> <p>2. Similarly genotoxicity studies (AMES and micronucleus tests) with the above formulation containing impurities have been conducted.</p>

NDA 21-445

<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>	<p>Yes</p>		<p>The route of administration in animal toxicity, carcinogenicity or in PK/TK studies is oral (dietary or gavage), which is the intended route in humans</p>
<p>8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m<sup>2</sup> or comparative serum/plasma AUC levels?</p>	<p>Yes</p>		<p>Yes, the draft labeling submitted in general is according to CFR and data express human dose multiples in mg/m<sup>2</sup> or AUC levels.</p>

ITEM	YES	NO	COMMENT
<p>9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.</p>	<p>Yes</p>		

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NDA 21-445

10) Reasons for refusal to file:

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Reviewing Pharmacologist: Indra Antonipillai

Supervisory Pharmacologist: Karen Davis-Bruno

File Name: 21445filing

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From the pharm/tox point, this application is filable  
It is a 45-day filing meeting checklist review, the  
application is filable

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## MEMORANDUM

**Date:** 18 October 2002

**From:** Bruce V. Stadel, MD, MPH  
Medical Officer

**Subject:** NDA 21445  
Addendum to Original Safety Review

**To:** The File

This Memo provides details regarding a patient who was discontinued from 1 of the 2 14-week Filter Coadministration randomized clinical trials (RCTs) of ezetimibe 10 mg. These RCTs are reviewed on pages 107-112 of the original Safety Review.

The patient was a 56-year old Caucasian woman who was discontinued from the Filter Coadministration RCT of ezetimibe 10 mg+atorvastatin compared to atorvastatin alone, due to adverse events of hepatitis and hemolytic anemia. She later died. She is referred to in the original Safety Review under serious adverse events on pages 108-109, and under discontinuations due to adverse events on page 110. She is not referred to as a study death because the death occurred a substantial interval of time after she was discontinued from the study. Details are as follows:

The patient entered the run-in phase of the RCT on 30 May 2001, and was treated with atorvastatin 10 mg/day. On 24 July (study day 1) she was randomized to the addition of ezetimibe 10 mg/day. On 3 September (study day 42), she reported a 5-day history of epigastric pain, for which she reported having taken Voltaren (diclofenac). Blood work on 3 September, by the central study laboratory, showed Hgb 10.7 g/dL, ALT 114 mU/mL, AST 37 mU/mL, Alk Phos 81 mU/mL, and Total Bili 2.25 mg/dL. On 4 September (study day 43), she was discontinued from the study; her last dose of study drug was on 2 September (study day 41). On 5 September (study day 44), a Coombs test was positive, Hgb was 9.1 g/dL and hemolytic anemia was diagnosed. On 14 November (study day 114), however, she was improved, with Hgb 12.8 g/dL, ALT 10 mU/mL, AST 14 mU/mL, Alk Phos 82 mU/mL, and Total Bili 0.19 mg/dL. The full NDA summary of the clinical trial findings is attached.

In March 2002, a family member reported that the patient had died, and that the autopsy revealed hemolytic anemia. At the time of death, the patient was reportedly being treated with simvastatin and cholestyramine resin.

An "Attendance Report" for the terminal illness was obtained from the \_\_\_\_\_ in the \_\_\_\_\_. The patient was admitted on \_\_\_\_\_ 2002 and died one day later. The diagnoses were: (1) systemic inflammatory response syndrome versus sepsis syndrome, (2) hemolytic anemia secondary to 1,

(3) coagulation disease due to consumption ?, (4) severe metabolic acidosis secondary to 1, (5) acute renal insufficiency, and (6) likely urinary tract infection due to septic gram-positive cocci (GPC). An addendum to the Attendance Report states that "The autopsy did not reveal guiding gross abnormalities related to the triggering process.... It would apparently be a hemolytic syndrome...." This is followed by a note which states that "The immunohematologic study concluded: positive direct Coombs test induced by IgG Ab, with a pattern that was not suggestive of drug induction."

Regarding the death, the time interval between the patient having stopped ezetimibe 10 mg on 2 Sep 01 and having died on — 02 appears to weigh against a relation to ezetimibe. According to a recent review, "Drug induced AIH [autoimmune hemolytic anemia] usually resolves within several days of discontinuing the medication, but occasionally requires months to fully resolve." Gehrs BC, Friedberg RC. Autoimmune Hemolytic Anemia. Am J Hematol. 2002;69:258-71.

On the other hand, regarding the initial event, the NDA states that "the sponsor cannot exclude the possible role of ezetimibe in this report of hepatitis and hemolytic anemia..." I agree with this conclusion, i.e., a role of ezetimibe in this report of hemolytic anemia and hepatitis appears unlikely but cannot be excluded.

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## ATTACHMENT

One subject in the EZ + Atorvastatin group (P00693-143/1793) discontinued due to Coombs'-positive hemolytic anemia associated with "hepatitis" of unknown origin. The event was considered by the investigator as serious, moderate in intensity, and possibly related to study medication (Section 10.1.1.2.). Because of the potential importance of this adverse event, a detailed summary appears in Table 51 below. In addition to the blood samples collected at the site during protocol-specified visits and analyzed by the central laboratory, the subject had samples collected and analyzed at local laboratories; these latter values do not appear in the central laboratory data base, but are included in the narrative below.

**Table 51** Detailed Information About "Hepatitis" in a Subject Who Received Ezetimibe and Atorvastatin: Filter Coadministration Pool

<b>Center:</b> P00693-143	<b>Sex:</b> Female
<b>Subject:</b> 1793	<b>Age:</b> 56
<b>Treatment and Regimen Assigned:</b> Ezetimibe and Atorvastatin	
<b>Reason for Summary:</b> 1. Study Discontinuation for Serious Adverse Events: Hemolytic Anemia, Hepatitis (15-Day IND Safety Report)	
2. ALT $\geq$ 3xULN on presumed consecutive occasions	

**Summary:** This 56-year-old Caucasian female was employed as an \_\_\_\_\_ She had a genetic diagnosis of Heterozygous Familial Hypercholesterolemia and a medical history positive for menopausal syndrome and asthma. She entered the lead-in phase of the study on 30 MAY 2001, receiving open-label atorvastatin 10 mg. The subject was not using any concomitant medications at this time. On 02 JUL 2001, the subject began to experience an adverse event of acute asthmatic bronchitis. This event was moderate in severity, unlikely related to study medication, and resolved on 06 JUL 2001 after treatment with the following concomitant medications, all taken 02-06 JUL 2001: deflazacort 30 mg BID, moxifloxacin 600 mg QD, fluticasone 100 mcg inhaled BID, salbutamol 100 mcg inhaled BID, formoterol 12 mcg inhaled BID, ipratropium bromide 20 mcg inhaled BID, and ranitidine 150 mg BID (gastric protection). Subsequently, the subject was randomized and received the first dose of the blinded study medication on 24 JUL 2001, while continuing on open-label atorvastatin 10 mg. On 15 AUG 2001, a second adverse event of asthmatic bronchitis began. This event was mild in severity, unlikely related to study medication, and resolved on 27 AUG 2001 after treatment with unspecified inhaled medications. On 03 SEP 2001 during a study visit, the subject complained of a five-day history of epigastric pain, radiating to the thorax and left hypochondrium. The symptoms were accompanied by epigastric pyrosis, food regurgitation, and intense malaise. The subject reported she took one suppository of what was originally reported as Nolotil (metamizole) on an unknown date for the pain; during follow-up it was established that the medication taken was actually Voltaren 100 mg on 30 AUG 2001. Lab work drawn at a hospital on 03 SEP 2001 showed elevated hepatic enzymes, anemia, leukocytosis, and small-form cells in the peripheral blood (WBC  $16.1 \times 10^9/L$ , HGB 101 g/L [10.1 g/dL], HCT 29%, SGOT [AST] 53 IU/L, SGPT [ALT] 176 IU/L, alkaline phosphatase 270 IU/L, and total bilirubin 44  $\mu\text{mol/L}$ ). Amylase and lipase were normal at 54 and 38 IU/L, respectively (normal ranges not provided). Blood work drawn the same day by the study center and analyzed by the central laboratory (see table below) confirmed the elevated enzymes, anemia, and leukocytosis (a one-time WBC elevation of  $18.7 \times 10^9/L$ , normal range  $4.8\text{--}10.8 \times 10^9/L$ ). A gastroscopy performed on 03 SEP 2001 revealed a very small hiatal hernia that did not explain the symptoms. The hiatal hernia was reported as an ongoing adverse event of mild severity, unlikely related to study medication, and treated with omeprazole 20 mg QD ongoing from 03 SEP 2001. An abdominal ultrasound performed on 03 SEP 2001 was normal. The subject was diagnosed with hepatitis, even though there were no medical history risk factors (alcohol, drug use, or travel) and hepatitis serology (A, B, and C) was negative. On 05 SEP 2001, a COOMBS

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