DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning See Table D-1 (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study SCH58235 Ezetimibe (*Name of clinical study*) (NDA-21445), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

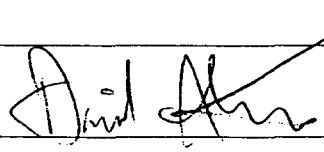
☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☑ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☑ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

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

Paperwork Reduction Act Statement

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zetia (ezetimibe) Tablets, 10 mg

Date of Application: December 27, 2001

Date of Receipt: December 27, 2001

Our Reference Number: NDA 21-445

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 25, 2002, in accordance with 21 CFR 314.101(a). If the application is filed as a standard review, the user fee goal date will be October 27, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). As discussed at the meeting of April 25, 2001, we are hereby granting a deferral of pediatric studies for patients ≥10 years of age and a waiver of pediatric studies on patients < 10 years of age.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. Please note

that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

We acknowledge your Proposed Pediatric Study Requests, submitted to IND —→ dated April 24, 2000, and September 26, 2001, and refer you to our letter dated November 1, 2001, which stated that before a written request could be issued, we would need to complete the review of the final study reports from Phase 3 studies of this drug submitted in a New Drug Application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manager
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/

William Koch
1/25/02 02:41:27 PM

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Office Director's Sign-Off Memorandum

Date:	Monday, October 21, 2002
NDA:	21-445
Sponsor:	Schering-Plough/Merck Partnership (S-P lead)
Proprietary Name:	Zetia (Ezetabimibe)

Introduction: This is a first-cycle application for this drug product, proposed for use in the treatment of hypercholesterolemia (either alone or in combination with HMG-CoA reductase inhibitors or 'statins'), including Homozygous Familial Hypercholesterolemia. It is also proposed for use in Homozygous Familial Sitosterolemia, a rare genetic disease characterized by excessive circulating plant sterols and premature atherosclerosis and cardiovascular death. The drug, a novel new molecular entity, blocks cholesterol and phytosterol absorption in the gut by mechanisms that have not been fully elucidated. However, the drug – both in animals and in humans – appears relatively selective for cholesterol and phytosterols, with a notable lack of inhibition of absorption of fat-soluble vitamins and oral contraceptives (e.g., estradiol/progeterones).

I refer the reader to the summary memorandum of Dr. David Orloff and that of Dr. Mary Parks for details. I am in substantial agreement with Dr. Orloff's observations, conclusions and recommendations. I will summarize selected important points, nonetheless, highlighting my review of the action package.

CMC: At the time of the review of the package, there were some minor CMC deficiencies listed as outstanding and needing to be addressed by the sponsor prior to approval. It now appears that the sponsor has already answered these deficiencies. If these answers are satisfactory, it then appears that the sponsor has provided sufficient data on the drug substance and product to allow for approval.

Final recommendations from Compliance on the acceptability of the EERs is pending.

Pharm/Tox: In preclinical models, this drug appeared to have some myocardial effects in rats and dogs, and hematologic effects in rats and renal effects in rats, albeit at very sufficiently high multiples compared to the human dose. No signal of any of these occurrences in the clinical studies has been seen. Combination studies were conducted that failed to identify a NOAEL and the findings largely were those typical of statin toxicity, with perhaps some enhancement of these toxicities in some cases. The reproduction studies showed some teratogenic effects in rats and rabbits (skeletal defects at high multiples of human exposure) that will require labeling and categorization as a "C." Both mutagenicity and carcinogenicity testing were negative.

Biopharmaceutics: Absolute bioavailability could not be performed due to solubility issues which resulted in the failure to develop ——————— However, the drug is orally bioavailable. Once absorbed, it is quickly glucuronidated, with this glucuronide accounting for 80 – 90% of the circulating ezetimibe. Both the parent and the conjugated drug actively inhibit cholesterol absorption. Both forms are also highly

protein-bound. It appears that much of the elimination of the drug is via the biliary system, with primarily fecal excretion. The half-life of the drug is approximately 22 hours, making it an appropriate once-daily drug. Food-effect studies showed no clinically important effects of food on absorption. Ezetimibe does not appear to induce or inhibit CYP P450 enzymes. The only remarkable issues with ezetimibe are:

- hepatic insufficiency greatly increases exposure to ezetimibe;
- binding resins (e.g., cholestyramine) were shown to bind ezetimibe and lead to decreased bioavailability of ezetimibe by approximately 50% or more when taken concomitantly; and
- one transplant patient on cyclosporine had very high levels of ezetimibe documented (12 fold increase) for unknown reasons.

Importantly, there are no remarkable PK interactions with the HMG CoA reductase inhibitors.

Clinical / Stastical: The sponsors conducted a very large clinical program in primary hypercholesterolemia, both to look at the efficacy of ezetimibe alone (two phase 3 studies), as well as in combination with a variety of statin drugs (four phase 3 studies). The efficacy of the drug appears remarkably consistent in either circumstance, with approximately 20% reductions in LDL cholesterol, 15% in total cholesterol, 15% in apo B, a small reduction in triglycerides of approximately 10% and a very small rise in HDL-C of approximately 2%. The amount of lipid lowering from adding ezetimibe is roughly similar to, if not somewhat better than, doubling the statin dose if not at the maximal range of that particular statin. It should be mentioned, however, that no outcomes data are yet available for this drug and there has been some recent supposition that the improvement in outcomes with statin therapy involves mechanism beyond lipid lowering, therefore, it cannot be concluded what the clinical effect of adding ezetimibe to a statin is relative to increasing the statin dose in patients with inadequate lipid lowering. Apart from the small trials in homozygous dyslipidemias discussed below, there are no adequate and well-controlled data on the use of ezetimibe with other lipid lowering drugs.

The sponsor also conducted specific studies in homozygous familial hypercholesterolemia and sitosterolemia, both of which showed efficacy in partially addressing the specific dyslipidemias of those conditions (i.e., in alleviating the laboratory abnormalities typical of the respective conditions).

The safety database for this drug was quite large (over 4500 patients), including approximately 1000 treated for more than 1 years duration. The safety experience with ezetimibe was remarkably good, with very few adverse events that looked clearly attributable to drug and none that appeared both severe and causally-related. This included the lack of a convincing signal of concern for such events as hepatitis/transaminitis (either ALTs or ASTs at levels of >= 3 x ULN were seen in 0.5% of placebo patients versus 0.8% of ezetimibe monotherapy patients), rhabdomyolysis, nor any cardiac, hematologic or renal that might have been predicted by preclinical models. There is a finding noted by Dr. Stadel in his safety review of a small numerical excess in individuals with rises in CPK in patients treated with ezetimibe compared to placebo (CPK >= 3 x ULN occurred in 1.3% of placebo patients vs. 2.1 % of ezetimibe alone

patients). However, there was no clinical signal that ezetimibe worsened any CPK effects of the statins, despite some data to that effect in animals.

A notable issue in this NDA is the lack of minority representation in the phase 3 studies, with fewer than 1% of all patients being Black/African American. While there were also very few Asians,

We will encourage the sponsor to undertake a phase-4 commitment to further study the efficacy and safety of ezetimibe both alone and in combination with a statin in the non-Caucasian population, particularly focusing on African-Americans/Blacks.

Based on the pre-approval wrap-up/safety review meeting with ODS in attendance, there are no unusual measures or specific considerations to the approval of this drug from the standpoint of risk management (other than the name – see below).

Labeling and nomenclature: Several cycles of labeling negotiations have been held with the sponsor and at this point, the labeling as amended looks satisfactory. It should be noted that DMETS has recommended against the name Zetia based on potential confusion with other medications, such as Zestril and Zebeta. However, the Division relayed these concerns to the sponsor, who then subsequently rebutted the concerns with data from a market analysis study and with considerations on the physical characteristics of the drug and the packaging. Further, the Division did not believe the consequences of the potential medication errors pointed out by DMETS would be serious. Therefore, the Division is accepting the name Zetia. I back that decision, but note that we will need to carefully monitor for any medication errors in the post-marketing period that might require intervention (e.g., a renaming).

Regulatory Conclusions: If acceptable recommendations are given for the EERs and the few outstanding substantive chemistry issues have been answered satisfactorily, this application will be given an "approval" action. Again, a phase-4 commitment to further study non-Caucasians for safety and efficacy is being sought from the company.

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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ON ORIGINAL

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/s/

Robert Meyer
10/21/02 03:46:40 PM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: October 3, 2002

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

TO: NDA 21-445
Zetia (ezetimibe)
Merck Schering Plough

SUBJECT: NDA review issues and recommended action

Background

Ezetimibe is a novel lipid altering agent that inhibits intestinal absorption of cholesterol and plant sterols. The precise mechanism of action is not known, though based on animal studies, its effect appears selective for cholesterol and plant sterols with no effect on fat soluble vitamins or steroid hormones. By indirectly depleting hepatic cholesterol stores, ezetimibe therapy results in increased clearance of LDL-C from the plasma.

The drug has been studied as part of combination therapy with a statin and is likely to be used primarily in this context. Whether used alone or in combination, the effects attributed to the single dose of ezetimibe proposed for marketing (10 mg daily) are the same, with approximate 18-20% mean reductions in LDL-C, 8-10% mean reductions in TG, and 2-3% mean increases in HDL-C.

The consistent additive effect on LDL-C lowering, the absence of intrinsic toxicity, and the absence of pharmacokinetic interactions with the statins make eze an attractive adjunct to statin therapy for LDL-lowering for the treatment of primary familial and non-familial hypercholesterolemia, for homozygous FH as an adjunct to apheresis, and for sitosterolemia, a condition characterized by hyperabsorption of plant sterols, high levels of LDL particles containing sitosterol, and accelerated atherosclerosis. The studies in these populations were submitted to the NDA, reviewed in full in the medical officers' reviews, and the results are summarized in labeling.

The drug has not been studied in patients with [redacted] Likewise, it has not been studied [redacted]

Clinical

NDA #
Drug:
Proposal:
10/25/02

Efficacy

The clinical efficacy data are thoroughly addressed in Dr. Temeck's review and summarized fully in Dr. Parks' review. The overall clinical trials database for this NDA is large, with 12 phase 2/3 double-blind, controlled trials completed and 4 ongoing open-label extension studies. The total exposure to eze in these trials, with durations out to 1 year, was over 1300, including ~2000 on monotherapy and ~1300 on eze plus statin.

As above, the efficacy of eze alone or in combination with statin with regard to LDL-C lowering was robust, consistent, and clinically significant in patients with primary hypercholesterolemia. The mean LDL-C lowering effect attributed to eze was approximately 18-20%. The effects of eze on TG and HDL-C were small in absolute magnitude, and variable from study to study due to small sample sizes. Overall the mean effects on TG were on the order of 8-10% reductions from baseline and on HDL-C approximately 1-3% increases from baseline.

In open-label trials, 33 patients with homozygous familial hypercholesterolemia were treated with atorva-eze or simva-eze combination therapy and 17 were treated with atorva or simva monotherapy. The overall additive effect of eze on LDL-lowering when given with high-dose statin compared to statin alone was between 15 and 20%. These findings are consistent with the findings in primary hypercholesterolemia and support the use of eze plus statin as adjuncts to apheresis and other therapeutic modalities in hoFH or if other therapies are unavailable.

Finally, 37 patients with sitosterolemia on various therapies were studied in an 8-week trial. 30 patients received eze and 7 received placebo in a blinded, randomized trial. The effect of eze on reducing sitosterol and campesterol levels was approximately 25%. The clinical effects of eze-induced changes in levels of these sterols in plasma has not been determined, and this is stated in labeling. Notwithstanding this, the changes relative to placebo are robust and establish eze as adjunctive therapy in this extremely rare, though serious condition.

Two issues related to efficacy and to labeling were raised during labeling negotiations with the sponsor and bear discussion here.

1. The sponsor originally proposed inclusion [redacted] in Indications [redacted]

[redacted]

So, we are comfortable with an approval that rests on the significant, large effect of eze on LDL-C, as time and again, the benefits of lowering LDL-C have been documented in clinical trials, regardless of mechanism,

[redacted]

Finally, we have approved a statin-niacin combination therapy in Advicor (Niaspan/lovastatin) which is intended for use in patients on lovastatin requiring further TG/HDL-C alterations. Likewise, we support the use of statin-fenofibrate combination therapy in the same manner. This approach is completely consistent with NCEP recommendations. Niacin and fenofibrate alone or in combination with statins produce large incremental changes in TG and HDL-C, of magnitudes that far exceed those of adding more statin or of adding eze. The clinical benefits associated with combination therapies of this type have not been studied in endpoint trials. However, there are endpoint data with fibrates and niacin alone that support hard clinical efficacy, and there are likewise multiple sources of data that support interventions to target elevated TG and non-HDL-C in at risk populations.

[redacted]

2. The sponsor has accepted our decision on the language contained in Indications.

[redacted]

The approach to labeling recommended by the division and accepted by the sponsor is as follows: The trials were powered to distinguish effects of eze vs.

comparator on LDL-C. Robust, significant effects were seen for LDL-C, as well as total-C, and apo B (closely correlated with LDL-C). Thus, we are approving the product based on satisfactory demonstration of efficacy. As in the statin labels, dating back to the original lovastatin labeling from 1987, effects on other lipid parameters, including TG and HDL-C, are presented in tables from dose ranging studies and others. These changes have not always been, study by study, statistically significant, but no distinctions have been thought necessary.

Safety

The safety database for eze is large, with 4584 patients exposed in clinical trials from phase 1-3. At the cutoff date for the NDA, 1341 patients had received eze for at least 6 months and 1018 received therapy for at least 1 year.

The drug appears not to be associated with significant side effects. As monotherapy or in combination with statin, there were no clinically significant instances of liver toxicity or myotoxicity, both relevant concerns for lipid altering agents generally (though with muscle a predominant concerns with statins and liver toxicity a concern with high-dose niacin). The incidence of consecutive elevations of transaminases > 3 X ULN was slightly increased among patients receiving statin plus eze combination therapy compared to statin alone, though eze monotherapy was not associated with a increased incidence of such events compared to placebo. There were no cases in any trial or treatment group of transaminase elevations > 10 X ULN. The incidence of marked CK abnormalities (> 10 X ULN) was actually higher in the statin monotherapy group than in the eze-statin combination therapy group. There were no cases of marked CK elevations with symptoms.

Dr. Stadel has pointed out in his review that the incidence of CK elevations >3 X ULN was higher among the small number of blacks than among Caucasians in this database, though he does not conclude that there is any effect of treatment on this phenomenon. Indeed, the usual cutoff for CK elevations is 10 X ULN precisely because of the non-specificity of lower level elevations. And as for elevations of lesser degree, there is no signal for an effect of eze on the incidence of these elevations. Apparently, the race-related finding is not unexpected based on literature. There are no recommendations for monitoring of CK levels for this drug (nor for statins). There is no evidence that ezetimibe has muscle toxicity. Myopathy is a clinical syndrome characterized by muscle symptomatology, and at least with statins, is felt to occur occasionally even in the absence of marked CK elevations.

Labeling

Labeling negotiations have been completed. Specific issues related to Clinical Studies and Indications have been resolved as discussed above.

Biopharmaceutics

OCPB finds the application acceptable. Ezetimibe is rapidly absorbed after oral administration. Absolute bioavailability was not determined due to the insolubility of the drug in aqueous media

The drug is extensively glucuronidated and undergoes enterohepatic recylcing. On the basis of animal studies, it would appear that the glucuronide is more potent as an inhibitor of intestinal cholesterol absorption than parent drug. The half-life of eze is approximately 22 hours. The drug is not an inhibitor or inducer of CYP450 enzymes. There is no pharmacokinetic interaction between eze and statins, fibrates, glipizide, digoxin, warfarin, and oral contraceptives. Cholestyramine administered concomitantly with eze reduced absorption based on AUC by 55%. No PK differences exist based on sex, age, race, body weight. Ezetimibe exposure was increased 50% in severe renal insufficiency and by 300% in severe liver disease. Eze is 94% bound to plasma proteins and this is not affected by severe renal disease or moderate hepatic disease.

Labeling recommends that ezetimibe not be used in patients with severe hepatic disease. No dosage adjustment is recommended for patients with renal disease.

Pharmacology/Toxicology

The organ toxicities in animals treated with eze alone occurred at large multiples of human exposures, with NOAELs providing >10X exposure multiples. The toxicity profiles of eze-statin combinations are interpreted by the toxicology team leader as exacerbations of statin toxicity Target organs for statin alone have been previously identified with statin monotherapy (liver, muscle) and confirmed in this program. There are metabolic interactions between statins and eze in the animal species studied (rat, dog, rabbit) that lead to increased exposures to statins and eze beyond those seen with monotherapy. No similar interactions were detected in humans. There is no specific toxicity of eze or eze-statin combination therapy identified in the preclinical studies.

Ezetimibe is labeled pregnancy category C based on findings in animals and no studies in pregnant women. The impact of combination therapy on the risk for embryo-fetal abnormalities is discussed based on the interactions cited above. The label refers the reader to the pregnancy labeling for statins if eze is to be used in combination in a woman of childbearing potential.

Chemistry/ Microbiology

The application is approvable from the standpoint of CMC. The manufacturing facilities inspections were satisfactory and all facilities received "acceptable" ratings.

A categorical exclusion from the environmental assessment was claimed by the sponsor and granted by the Agency.

DSI/Data Integrity

Two clinical sites were audited. A Form 483 was issued to Dr. McGarry for minor deficiencies. The DSI recommendation was that the data submitted from the two investigators were acceptable for review.

Financial disclosure

The financial disclosure information is in order as reviewed by Dr. Temeck. There are no reasons to question the validity of the data submitted in the application.

ODS/nomenclature

DMETS does not recommend the tradename "Zetia" based on a number of sound-alike, look-alike drugs. The sound-alike/look alike concerns with Zebeta (bisoprolol) were addressed by the sponsor in a submission to the division. Based on results of marketing analysis, comparison of the physical characteristics of the drug products, and differences in packaging, the sponsor concluded that there was a low probability of medication errors. Dr. Parks accepts the sponsor's response, and I concur. DMETS also expressed concern over sound-alike/look alike confusion with Zestril (ACE inhibitor). Clearly, many patients eligible for Zetia will be treated with beta-blockers and ACE inhibitor. Therefore, it is worth considering the consequences of medications errors involving these agents. First, the lipid metabolic effects and blood-pressure/pulse/electrolyte effects of an error which substituted a beta-blocker or ACE inhibitor, at doses intermediate in the adult dosing range for the two drugs, in lieu of ezetimibe, would not likely adversely affect the patient in the short run. Likewise, the effects on blood pressure, heart rate, electrolytes, and lipids of an error which substituted ezetimibe, which has no side effects to speak of, in lieu of a beta-blocker or ACE inhibitor, while potentially noticeable by the patient and the physician, are unlikely to adversely effect the patient in the short run. In sum, the name Zetia is acceptable.

Recommendation

Approve. CMC deficiencies are cited in the action letter and will need to be addressed prior to approval.

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/s/

David Orloff
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MEDICAL OFFICER

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NDA 21-445

Zetia (ezetimibe) Tablets 10 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: MSP Singapore Co., LLC
21 Thas Ave. 6
Singapore 637766
Representative:
Joseph Lamendola
Schering Corp.

Indication: Primary Hypercholesterolemia

Monotherapy

ZETIA, administered alone is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Combination therapy with HMG-CoA reductase inhibitors

ZETIA, administered in combination with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, and Apo B in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH)

The combination of ZETIA and atorvastatin or simvastatin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia

ZETIA is indicated as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia

Presentations: HDPE bottles 30, 90 and 500 count
Blisters 10 per card X 10 (100 count)
Physician sample blister 7 count

EER Status: Acceptable 22-OCT-2002

Consults: ODS – Re-review of propriatary name "Zetia" – acceptable 8/22/02

DRUG SUBSTANCE: Ezetimibe, 1-(4-fluoropenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, is a new molecular entity manufactured by Schering-Plough LTD, Singapore Branch. The API has three chiral

centers with the stereochemical configuration — Ezetimibe (SCH 58235) was synthesized by
[ ]

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

Based on data from ICH stability studies on 8 lots, the drug substance is stable for at least 24 months at room temperature when stored in ———

DRUG PRODUCT: The drug product is manufactured by Schering-Plough Products (Las Piedras, PR). The proposed commercial formulation for ezetimibe is a white to off-white capsule shaped, embossed, uncoated immediate release tablet. Each tablet contains 10 mg of ——— ezetimibe combined with lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate and is manufacture via a ——— Excipients are USP/NF grade. The manufacturing process and in-process controls are described in detail.

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

Stability data through 24 monthe for 3 batches and addition batches through 15 and 18 months support a 24 month expiry. A waiver is acceptable for the environmental assessment. Labels and labeling are acceptable.

Minor deficiencies were noted, which will be sent in an advice letter immediately following approval.

Over-All Conclusion
From a CMC perspective an approval action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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Eric Duffy
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CHEMIST

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MEMORANDUM

DATE: October 22, 2002

SUBJECT: CGMP Inspection

TO: File of NDA #21-445 (Zetia)

FROM: Chien-Hua Niu, Ph.D.

THROUGH: Dr. Stephen Moore, Chemistry Team Leader, HFD-510

CGMP inspection of the manufacturing site for the drug substance (Schering Plough Corp., 50 Tuas West Dr.. Singapore) has been completed and found to be acceptable by the Office of Compliance (see the attached). Therefore, the application can be approved from chemistry viewpoint.

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21445/000
Priority: 1S
Org Code: 510
Stamp: 27-DEC-2001 Regulatory Due: 27-OCT-2002
Action Goal:
District Goal: 28-AUG-2002
Applicant: MSP SINGAPORE
C/O SCHERING CORP
2000 GALLOPING HILL RD
KENILWORTH, NJ 07033
Brand Name: ZETIA (EZETIMIBE) 10 MG TABLETS
Established Name:
Generic Name: EZETIMIBE
Dosage Form: TAB (TABLET)
Strength: 10 MG

FDA Contacts: C. NIU (HFD-510) 301-827-6420 , Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation:

Establishment: 2650155
SCHERING CORP
PRIDCO INDUSTRIAL PARK SR 83
LAS PIEDRAS, PR 00671
DMF No:
AADA No:

Profile: TCM
OAI Status: OAI ALERT
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-SEP-2002
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: 9614153
SCHERING PLOUGH CORP
50 TUAS WEST DR
SINGAPORE, , SN 638408
DMF No:
AADA No:

Profile: CSN
OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-OCT-2002
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER

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/s/

Chien-Hua Niu
10/23/02 08:39:20 AM
CHEMIST

Duu-gong Wu
10/23/02 01:04:23 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

REQUEST FOR CATEGORICAL EXCLUSION FROM ENVIRONMENTAL ASSESSMENT

Pursuant to 21 CFR Part 25

Ezetimibe Tablets, 10 mg

DATE: December 18, 2001

NAME OF APPLICANT: MSP Singapore Co. LLC

ADDRESS: c/o Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Contact: Nicholas J. Pelliccione, Ph.D
Telephone: 908-740-5680

DESCRIPTION OF THE PROPOSED ACTION

MSP Singapore Co. LLC is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for Ezetimibe Tablets, 10 mg pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act. Such an exclusion is provided in 21 CFR 25.31(b) for action on a new drug application (NDA) if "the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion." Extraordinary circumstances as referred to in 21 CFR 25.21 do not apply.

Ezetimibe Tablets, 10 mg is a new drug to be used for treatment of hypercholesterolemia. Information is provided below to justify exclusion from the requirements of an environmental assessment.

IDENTIFICATION OF THE DRUG SUBSTANCE

Established Name: Ezetimibe

Brand Name: To be determined

Chemical Name: 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone

Registry Number: CAS 163223-33-1

Molecular Formula: $C_{24}H_{21}F_2NO_3$

Molecular Weight: 409

INTRODUCTION OF THE SUBSTANCE INTO THE ENVIRONMENT

Information on the estimated concentration at the point of entry into the aquatic environment is provided in Confidential Appendix 1.

JUSTIFICATION FOR EXCLUSION

The concentration of the substance that will be entering the aquatic environment is estimated to be less than 1 part per billion. Controls will be exercised over the disposal of waste material so that no significant effect on the environment is anticipated. Therefore, the applicant requests a categorical exclusion from the requirements of an environmental assessment as provided in 21CFR 25.31(b).

CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the MSP Singapore Co. LLC.

Appendix 1 of this document contains information which is considered confidential in nature and is therefore not releasable to the public. The undersigned official certifies that the body of this request for exclusion contains nonconfidential information and understands that this information will be made available to the public in accordance with 40 CFR 1506.6.

Date: 12/18/2001

By: J Nusser

Joseph A. Nusser, P.E.
Senior Director Environmental
Compliance and Projects
Schering Corporation
for MSP Singapore Co. LLC

APPEARS THIS WAY
ON ORIGINAL

Executive CAC
Date of Meeting: April 16, 2002

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
Abigail Jacobs, Ph.D., HFD-540, Alternate Member
Robin Huff, Ph.D., HFD-570, Alternate Member
Karen Davis Bruno, Ph.D., HFD-510, Team Leader
Indra Antonipillai, Ph.D., HFD-510, Presenting Reviewer

Author of Draft: Indra Antonipillai

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: NDA 21-445, IND ——
Drug Name: Zeita (Ezetimibe) tablets
Sponsor: MPS Singapore CO., LLC, Singapore. Joint venture between Merck & Co. and Schering Corp.

Background:
Zeita is a cholesterol absorption inhibitor. Its mechanism of action is unknown but it acts locally in the intestine to block the intestinal absorption of cholesterol and related phytosterols. It is indicated alone, or in combination with statins for primary hypercholesterolemia (heterozygous and ——— familial) and for homozygous familial sitosterolemia. The drug is mainly metabolized to glucuronide, which has as much or more drug activity than the drug itself.

Mouse carcinogenicity study

In a 2-year carcinogenicity study in mice (Crl:CD(CR)BR, 50/sex/dose), doses of 25, 100, 500 mg/kg/day were administered in a diet for 104 weeks. No AUC values of the total drug (parent + glucuronide metabolite) were provided but plasma concentrations of the total drug were provided which increased with doses (males 0.21, 1.8, and 14.1 µg/ml, females 0.61, 5.7 and 31.3 µg/ml at 25, 100, 500 mg/kg/day respectively).

The Exe Cac Committee had previously concurred with the sponsor on doses selected for the present cac study. The highest dose selection (500 mg/kg/day) for mouse CAC study was based on saturation of exposure to the parent drug, which at 500 and 2000 mg/kg/day was 0.98 and 0.95 µg.h/ml in males, and 0.33 and 0.35 µg.h/ml in females respectively in a 3-month dose range study in mice. At 500 mg/kg/day, the exposure to parent compound and the major metabolite glucuronide (males 216, females 347 µg.h/ml) was 166-267 fold the human dose at 20 mg/day (1.3 µg.h/ml, based also on AUC of a parent + metabolite). The current clinical dose in humans is 10 mg/day. Also the dietary route was chosen, as exposures of the parent drug + metabolite were higher by this route —— µg.h/ml) vs. gavage (—— µg.h/ml).

In the present carcinogenicity study, no AUC values of the total drug (parent + glucuronide) were provided to determine if the saturation of absorption was achieved, as

was concurred by the Exe. CAC committee in the dose selection protocol. However in the present study approximately 3 fold higher plasma concentrations were achieved (males 14.1 µg.h/ml, females 31.3 µg.h/ml) vs in the 3-month mouse study (males 4.4, females 9.2 µg/ml) which already showed exposures 166-267 fold the human doses.

No neoplastic findings were observed in mice with the drug compared to control. Oral dosing for 2 years at 25, 100 and 500 mg/kg/day did not result in a significant increase in neoplastic or non-neoplastic findings in mice. In females, malignant histiocytic sarcoma (at undetermined primary site) was observed at a higher number in 25 mg/kg/day group (4, 7, 11, 3 and 6 at 0, 0, 25, 100, 500 mg/kg/day respectively), but no dose related trend was observed, and was not statistically significant. In males in harderian gland, increased incidences of benign adenomas were noted specially at low doses (0, 2, 9, 3, 4 at 0, 0, 25, 100, 500 mg/kg/day respectively, in females these incidences were 2, 3, 3, 1, 4 respectively), but were not statistically significant in the trend analysis.

Rat carcinogenicity study

A 2-year dietary carcinogenicity study in rats (Crl:CD (SD)BR, 50/sex/dose) was conducted, where doses of 150, 750, 1500 mg/kg/day were administered to males, and 50, 250, 500 mg/kg/day to females in a diet for 104-106 weeks. All animals were diet restricted and received 25% less food/day. AUC values (0-12 hrs) of the total drug (parent + glucuronide metabolite) poorly correlated with doses (males 4.1, 4.4, 4.8 µg.h/ml at 150, 750, 1500 mg/kg/day respectively, females 3.3, 6.0, 6.7 µg.h /ml at 50, 250, 500 mg/kg/day respectively).

Again, the Exe Cac Committee had concurred with the sponsor's dose selection for the present cac study. The highest dose selection in the rat CAC study (1500 mg/kg/day in males and 500 mg/kg/day in females) was based on saturation of exposure (AUC_{0-24h}) to the parent drug + glucuronide in a 3-month study in rats, which was achieved at 1500 mg/kg/day in males (AUC exposures were 3.1, 4.7, 7.7, 11 µg.h/ml at 0, 20, 100, 500, 1500 mg/kg/day) and at 500 mg/kg/day in females (1.3, 7.3, 12, 13 µg.h/ml respectively). as no increases in plasma conc. occurred after 500 mg/kg/day. However these values provided the exposures of only 6-9 fold the human doses at 20 mg/day (1.3 µg.h/ml, based also on AUC of a parent + metabolite). In a 2-week study in diet restricted rats (with 25% less food), exposure to the total drug was not different at 2000 mg/kg/day (males 10.6, females 15.8 µg.h/ml) compared to that in a 3-month study in non-diet restricted rats at 1500 mg/kg/day (males 11, females 13 µg.h/ml), suggesting that plateau in exposure had been reached in males and females. Also the dietary route was chosen, as exposures of the parent drug + metabolite were higher by this route (—— µg.h/ml) vs. gavage (—— µg.h/ml).

In the current rat carcinogenicity study, saturation of absorption of the drug (AUC_{0-12h}) was achieved in the male rats at the lowest dose of 150 mg/kg/day, as exposures did not further increase with increase in dose to 750-1500 mg/kg/day (4.1,4.4, 4.8 µg.h/ml at 150, 750, 1500 mg/kg/day respectively), while in females this was achieved at a mid dose of 250 mg/kg/day (values were 3.3, 6.0, 6.7 µg.h/ml at 50, 250, 500 mg/kg/day respectively).
The drug decreased body weights (of 4-7%) and weight gains (of 7-10%) in males at mid/high doses during most of the study weeks. In female rats, hepatocellular adenomas

were observed in 2/50 animals (or 4%) at high dose vs. none in control or other groups. Sponsor states (in the initial submission on 12/27/2001) that these are in the range of historical control values (range 1-5.5%). However the reference for historical control data appears to be in the rats which are not diet restricted (Spontaneous neoplastic lesions and selected non-neoplastic lesions in the Crl:CDBR rats, ——— ——— Feb, 1992). Sponsor states that no statistically significant trend in the incidence of tumor-bearing rats was observed with increases in drug doses, and the drug (SCH 58235) tested negative in both sexes (up to doses of 1500 mg/kg/day in males, and 500 mg/kg/day in females) in the 2-year rat carcinogenicity study.

In summary, oral dosing for 2 years in rats at 150, 750, 1500 mg/kg/day in males and 50, 250, and 500 mg/kg/day in females did not result in significant increase in neoplastic or non-neoplastic findings. However, this is contingent on follow up of the two hepatocellular adenomas observed in the high dose female group, which was communicated to the sponsor in a T-con on 5/23/2002.

In a subsequent 7/3/2002 submission, sponsor has provided the historical tumor incidences data in control diet restricted rats. No hepatocellular adenomas were observed in male or female animals in control diet restricted rats. The sponsor considers the ——— databases more appropriate historical control data set for ezetimibe studies since their own database is limited to 100 diet restricted rats/sex/group. The ——— databases in the diet restricted rats (Spontaneous neoplastic lesions and survival in the Crl:CD(SD) BR rats maintained on dietary restriction, ——— March, 1998) show that incidence of hepatocellular adenomas in female rats are in the range of 0-8% (mean 2.2%) which is derived from 26 total studies, and in 20 studies lesions were identified. This suggests that hepatocellular adenomas of 4% in the current carcinogenicity study in female rats are incidental.

Executive CAC Recommendations and Conclusions:

Mouse
The study protocol was acceptable, as it had received prior concurrence from the Exec CAC committee. The Committee concluded that there were no significant tumor findings in the 2-year mouse CAC study.

Rat:
The study protocol was acceptable, having received prior concurrence from the Exec CAC committee. After reviewing both the sponsor's and ——— historical control dataset in diet restricted rats, the committee concluded that a 4% increase in tumor incidences in hepatocellular adenomas in female rats at a high dose was incidental. In conclusion, The Committee concurred that there were no significant tumor findings in a 2-year diet restricted rat CAC study.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:/
/Division File, HFD-510, NDA 21-445, / HFD-510 Davis Bruno
/HFD-510 Antonipillai, /HFD-510, Koch, /HFD-024, Seifried

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/s/

Joe Contrera
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APPEARS THIS WAY
ON ORIGINAL

MEDICAL TEAM LEADER'S MEMO OF NEW DRUG APPLICATION

NDA 21-445
Drug product: Zetia ® (ezetimibe)
Drug sponsor: Merck Schering Plough
Indication: Lipid-altering in the following categories:

- **Primary Hypercholesterolemia**
- **Homozygous Familial Hypercholesterolemia**
- **Homozygous Sitosterolemia**

Primary Medical Reviewers: Jean Temeck, MD (efficacy) and Bruce V. Stadel, MD, MPH (safety)

EXECUTIVE SUMMARY

Ezetimibe is a lipid-altering agent which acts, at least in part, by inhibiting the intestinal absorption of dietary and biliary cholesterol through an unknown mechanism of action. The clinical development program for this compound targeted treatment of the following conditions:

1. **primary hypercholesterolemia**, where ezetimibe was studied as both monotherapy and combination therapy with statins,
2. **homozygous familial hypercholesterolemia**, where ezetimibe was studied in combination with a statin approved for this same indication, and
3. **homozygous sitosterolemia**, where ezetimibe was given on top of other accepted therapies for this rare condition

Primary hypercholesterolemia is an established risk factor for cardiovascular disease and the reduction in LDL-C and total-C with a variety of lipid-altering therapies has been associated with a reduction in the risk of CV mortality and morbidity. In this NDA, the sponsor evaluated the safety and efficacy of ezetimibe monotherapy and its combined use with a statin in affecting markers of CV disease risk in 7 phase 3 clinical studies. LDL-C reduction was the primary efficacy measure with other components of the lipid profile being secondary efficacy measures.

From the pooled results of two studies, ezetimibe monotherapy provided effective LDL, total-C, and apo-B lowering with mean reductions from baseline of –17%, -13%, and –14%, respectively. The effects of monotherapy on TGs and HDL-C were variable with mean changes of –8% and +3%, respectively. In a pooled analysis of all statin-treated groups across all doses studied, the addition of ezetimibe to on-going statin therapy reduced LDL-C by an average of –21% over statin monotherapy while the concurrent initiation of ezetimibe and a statin reduced LDL-C by an average of –14% over statin monotherapy.

Homozygous familial hypercholesterolemia (HoFH), an autosomal dominant disorder in which affected individuals inherit two mutant alleles for the LDL receptor, is characterized by markedly elevated cholesterol levels (e.g., LDL > 500 mg/dL) and premature CVD presenting in childhood. Death before age 20 years is not uncommon. Treatment options include LDL-apheresis, liver transplantation, and rarely, portacaval anastamosis. Two statins (atorvastatin and simvastatin) currently have an approved

indication for treatment of HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL-apheresis) or if such treatments are unavailable.

One clinical study in this NDA demonstrated that the addition of ezetimibe 10 mg to atorvastatin or simvastatin 40 or 80 mg daily resulted in an average further reduction in LDL-C of –14 to –21% compared to continuing on the statin monotherapy.

Homozygous sitosterolemia is a rare condition in which increased absorption of dietary plant sterols results in accelerated atherosclerosis. There are currently no approved drug treatments for this disease; however, bile-acid sequestrants have been used off-label with varying degrees of efficacy reported in the published literature. Ezetimibe therapy added to diet or current stable treatment regimens resulted in mean plant sterol reductions of –21 and –24% for plasma sitosterol and campesterol, respectively.

The safety of ezetimibe monotherapy and its combined use with statins was evaluated in controlled trials of maximum 3 months duration. Open-label extension studies provided additional safety data with the median duration of use for monotherapy and combination therapy being 18.5 months and 11.6 months, respectively. From a database comprised of 4,584 patients exposed to ezetimibe therapy there were no significant differences in the incidences of clinical adverse events, serious or resulting in discontinuation, between placebo and the different ezetimibe treatments. The addition of ezetimibe to statin therapy did result in higher frequencies of ALT and/or AST elevations compared to statin monotherapy, ezetimibe monotherapy, and placebo but none of these cases resulted in a clinical adverse event. The co-administration of ezetimibe and statin did not result in a greater frequency in CK elevation compared to statin monotherapy.

Drs. Temeck and Stadel emphasized in their reviews the low number of non-Caucausians studied in this NDA. Although the efficacy review suggests an attenuation of LDL-lowering associated with ezetimibe therapy in non-Caucasians, this finding is not consistent in all studies and the small sample sizes limit any conclusion on the true efficacy of ezetimibe in these patients. For example, one monotherapy study showed no difference between ezetimibe and placebo regarding LDL-lowering in the non-Caucasian subgroup whereas in a second study the placebo-subtracted effect of ezetimibe was greater in Caucasians versus non-Caucasians. In general, a trend in cholesterol lowering is still observed in the non-Caucasian groups. Dr. Stadel's review of safety by race revealed a higher incidence of CK elevations in Blacks versus other ethnic groups; however, the frequency was not markedly different between treatment and placebo and no clinical adverse event resulted from these laboratory abnormalities. To the extent that lipid-altering efficacy of ezetimibe can be monitored in patients through routine bloodwork and the safety review suggests a similar profile between treatment and placebo, a Phase 4 study in non-Caucasians is not required as a condition of approval for this application. The label should discuss the limited data available in non-Caucasians.

Overall, the review of the medical efficacy and safety support an adequate risk-benefit profile for ezetimibe monotherapy and its combined use with a statin in the proposed indications. Pending labeling negotiations, this application should be approved.

PRECLINICAL

Please refer to Dr. Indra Antonipillai's review of the preclinical pharmacology and toxicology results.

As discussed in Dr. Temeck's review the animal toxicology studies revealed the heart and lymph node as major target organs of toxicity in the 1 and 6-month monotherapy studies in dogs and rats. However, these findings were observed at 7 to 18x the human exposures and heart toxicity was not observed in the 1-year dog study.

In preclinical combination ezetimibe and statin studies, main target organs of toxicity were liver, stomach, and skeletal muscles with no NOAELS established in the rat and dog studies. Although the absence of a safety margin in preclinical studies is a concern, the clinical studies involving ezetimibe and statins have not revealed a marked difference in overall safety between the combination treatment versus monotherapy or placebo (see Dr. Stadel's review on clinical safety and summary below).

CLINICAL PHARMACOLOGY

Please refer to Dr. Wei Qiu's review from the Office of Clinical Pharmacology and Biopharmaceutics for detailed summaries of the clinical pharmacology studies submitted to this NDA. The results of her review have also been summarized by Dr. Jean Temeck under Section III of the primary medical review.

Briefly, ezetimibe is an insoluble drug that has been [redacted] solubility and absorption. The drug undergoes glucuronidation to form an active metabolite representing 80 to 90% of total drug in plasma. There is also extensive enterohepatic recirculation. The parent compound (ezetimibe) and the metabolite (ezetimibe glucuronide) combined have a half life of approximately 22 hrs.

Drug interaction studies show:

- no significant interaction between ezetimibe and statins while fibrates increase the exposure of total ezetimibe by 50 to 70%
- no significant effects on the activity of CYP1A2, 2C8 or 2C9, 2D6, or 3A4

Studies in special populations show:

- a 4-fold increased exposure in patients with moderate and severe liver disease
- a 2-fold increased exposure in elderly patients
- similar pharmacokinetic profile across gender, race (Caucasians vs. Blacks), and body weight
- a possibility for cyclosporine interaction noted based on a finding of 9-fold increase in ezetimibe levels in one patient (drug interaction study with cyclosporine submitted to IND)

SUMMARY OF CLINICAL STUDIES

There were 12 Phase 2/3 double-blind, placebo- or active-controlled trials and 4 ongoing open-label, extension studies submitted to this NDA. These studies are summarized in the following table:

Table 1. Summary of Phase 2/3 Clinical Studies Submitted in Support of Proposed Indications

Protocol No.	Study Description	Total No. Patients/ Duration of Treatment	Ezetimibe-only Exposures	Ezetimibe + Statin Exposures
Phase 2 Ezetimibe Dose Response Studies				
C96-411/C96-345	Pilot dose-ranging study of the safety and efficacy of ezetimibe compared to pbo and lovastatin in patients w/ primary hypercholesterolemia	124 8 wks	89 (18 at 10 mg)	0
C98-010	DB, dose-response study of the efficacy and safety of 4 doses of ezetimibe compared to pbo in patients w/ primary hypercholesterolemia	243 12 wks	191 (46 at 10 mg)	0
C98-258	DB study of efficacy and safety of am vs pm dosing of 2 doses of ezetimibe compared w/ pbo in patients w/ primary hypercholesterolemia	189 12 wks	153	0
Phase 3 Ezetimibe Monotherapy Studies in Primary Hypercholesterolemic Patients				
P00474	DB efficacy and safety study of ezetimibe 10 mg compared with pbo	827 12 wks	622	0
P00475	DB efficcy and safety study of ezetimibe 10 mg compared with pbo	892 12 wks	666	0
Phase 3 Ezetimibe/Statin Coadministration Studies in Primary Hypercholesterolemic Patients				
P00679	DB efficacy and safety study of ezetimibe 10 mg in addition to lova compared w/ pbo	548 12 wks	72	192
P00680	DB efficacy and safety study of ezetimibe 10 mg in addition to simva compared w/ pbo	668 12 wks	61	274
P00691	DB efficacy and safety study of ezetimibe 10 mg in addition to prava compared w/ pbo	538 12 wks	64	204
P00692	DB efficacy and safety study of	628 12 wks	65	255

Table 1. Summary of Phase 2/3 Clinical Studies Submitted in Support of Proposed Indications

Protocol No.	Study Description	Total No. Patients/ Duration of Treatment	Ezetimibe-only Exposures	Ezetimibe + Statin Exposures
	ezetimibe 10 mg in addition to atorva compared w/ pbo			
Phase 3 Ezetimibe/Statin Coadministration Add-on to Statin Background Study				
P02173/P02246	DB, rand., PC study to evaluate efficacy and safety of ezetimibe when added on to ongoing statin therapy in patients w/ primary hypercholesterolemia, known CHD, or multiple CV risk factors	769 data available for initial 8 wks of therapy	0	379
Phase 3 Ezetimibe Studies in HoFH or Homozygous Sitosterolemic Patients				
P01030	Ezetimibe + atorva and simva in the therapy of HoFH	50 12 wks	0	33
P02243/P02257	Rand., DB, PC study of safety and efficacy of ezetimibe added to current treatment of patients with homozygous sitosterolemia	37 8 wks	30	7
Total		**5,513**	**2,013**	**1,337**
On-going Open-Label Extension Study				
P00476 (extension to P00474/P00475)	long-term, OL safety and tolerability study of ezetimibe in subjects w/ primary hypercholesterolemia	1313 24 months	783	530
P01416 (extension to P00691)	long-term, OL safety and tolerability study of ezetimibe in subjects w/ primary hypercholesterolemia	321 12 months	0	321
P02134 (extension to P00679 or P00680)	long-term, OL safety and tolerability study of ezetimibe in addition to simvastatin in subjects with primary hypercholesterolemia	359 12 months	0	359
P01417 (extension to P01030)	long-term, OL safety and	45 24 months	0	45

Table 1. Summary of Phase 2/3 Clinical Studies Submitted in Support of Proposed Indications

Protocol No.	Study Description	Total No. Patients/ Duration of Treatment	Ezetimibe-only Exposures	Ezetimibe + Statin Exposures
	tolerability study of ezetimibe in addition to atorvastatin or simvastatin in the treatment of HoFH			

A total of 5,513 patients were enrolled in the 8 to 12-week controlled trials with 2,013 exposed to ezetimibe alone and 1,337 to ezetimibe + statin combination therapy.

REVIEW OF CLINICAL TRIALS

Indications Sought and Proposed Labeling

A in-depth review of the efficacy results is provided by Dr. Jean Temeck in her primary review. This secondary review will focus only on those results addressed in the sponsor's proposed labeling. The proposed labeling includes the following indications and relevant sections of the label describing the supportive study findings:

1. Primary Hypercholesterolemia (familial and non-familial)

   Under this indication, the sponsor seeks approval for the monotherapy use of ezetimibe and its coadministration with a statin. The studies supporting these claims include P00474 and P00475 for monotherapy use and P00679, P00680; P00691, P00692, and P02173 for the coadministration with statin.

   The efficacy measures from these trials summarized under the CLINICAL STUDIES section of labeling include the effects of therapy on LDL-C, total-C, apoB, TG, and HDL-C. In addition, the sections describing combination therapy include [and a claim that ezetimibe in combination with the lowest dose of a statin provided similar or greater LDL-C reduction compared to the highest test dose of the same statin administered alone.

2. Homozygous Familial Hypercholesterolemia (HoFH)

   Under this indication, ezetimibe is to be used with an approved statin with or without other available therapies (e.g., LDL apheresis) for this same indication to reduce total-C and LDL-C.

3. Homozygous Sitosterolemia

   Under this indication, ezetimibe is recommended for the reduction of elevated sitosterol and campesterol levels in patients with homozygous sitosterolemia.

Efficacy Results

Primary Hypercholesterolemia

Dose-Response Studies

The 3 phase 2 studies evaluated dose response for ezetimibe monotherapy in doses ranging from ——— mg daily in primary hypercholesterolemic patients. Based on these results, ezetimibe 10 mg was evaluated further in the phase 3 pivotal trials as doses higher than 10 mg produced only marginal incremental reductions in LDL-C relative to the increase in dose and doses less than 10 mg achieved an LDL-lowering of > 15% from baseline in only a small proportion of patients. This secondary efficacy review will refer only to ezetimibe at the 10 mg dose. Unless otherwise stated, reference to ezetimibe or EZ implies its use at the 10 mg dose.

Ezetimibe Monotherapy

Data for lipid-altering effects of ezetimibe monotherapy were available from the 2 Phase 3 monotherapy studies, P00474 and P00475. The results are summarized in the following table:

Table 2. Mean Response to Ezetimibe Monotherapy in Primary Hypercholesterolemia

	Calc. LDL-C		Total-C		HDL-C		TGs*		Apo-B	
	Placebo	EZ	Placebo	EZ	Placebo	EZ	Placebo	EZ	Placebo	EZ
P00474										
N	205	622	205	622	205	622	205	622	205	620
Baseline Mean, mg/dL	163.5	164.4	248.7	249.1	51.0	52.1	171.2	163	160.6	161.3
Mean % Chg from baseline (SEM)	+1.4 (0.8)	-18.2 (0.5)	+0.6 (0.6)	-12.4 (0.4)	-1.3 (0.8)	+1.0 (0.5)	-1.2	-7.3	-1.0 (0.8)	-15.4 (0.5)
`0475										
	226	666	226	666	226	666	226	666	225	662
Baseline Mean, mg/dL	167.5	166.9	254.5	252.8	52.2	52.1	174.8	169	164.4	164.2
Mean % Chg from baseline (SEM)	+1.1 (0.8)	-17.7 (0.5)	+0.8 (0.6)	-12.5 (0.4)	-1.6 (0.7)	+1.3 (0.5)	+2.2	–9.3	-1.4 (0.8)	-15.5 (0.5)

*efficacy measure for TGs presented as median % change from baseline

The differences in mean % changes from baseline in LDL-C, total-C, HDL-C and apoB between ezetimibe and placebo were significant ($p<0.01$ or <0.05). The difference in the median % changes from baseline in TGs between the two treatment groups was significant in P00475 but not for P00474.

Overall, these two studies show similar lipid-altering changes associated with ezetimibe 10 mg daily use. The pooling of the 2 study results also provided similar data. The sponsor proposes to present data from the individual studies and the pooled data.

Ezetimibe/Statin Co-administration

The efficacy of ezetimibe/statin co-administration was evaluated in 2 different clinical scenarios: the concurrent initiation of these 2 lipid-altering drugs (P00679, P00680, P00691, and P00692) or the addition of ezetimibe to on-going statin therapy (P02173/P00246).

Effects on LDL-C with the Concurrent Administration of Ezetimibe and a Statin

The concurrent initiation of ezetimibe with 4 different marketed statins (lovastatin, simvastatin, pravastatin, and atorvastatin) provided incremental LDL-lowering over the individual constituents given alone. The LDL-lowering results for each study are summarized in the following tables:

Table 3. Mean Percent Change in LDL-C from Baseline in P00679 (Eze/Lovastatin Co-administration) Study

	Placebo n=64	EZ n=72	Lova 10 n=73	EZ + Lova 10 n=65	Lova 20 n=74	EZ + Lova 20 n=62	Lova 40 n=73	EZ + Lova 40 n=65
Baseline LDL, mg/dL	177.8	178.0	177.3	173.5	175.6	175.7	179.7	178.1
Mean % Chg from baseline (SEM)	-0.03 (1.7)	-18.6 (1.6)	-19.0 (1.6)	-33.1 (1.7)	-26.0 (1.6)	-39.4 (1.8)	-29.2 (1.6)	-44.5 (1.7)
Difference from same dose of statin-alone in mean % chg from baseline (95% CI)	NA	NA	NA	-14.2 (-18.8, -9.5)	NA	-13.5 (-18.2, -8.8)	NA	-15.3 (-20.0, -10;7)

In P00679, the co-administration of ezetimibe 10 mg to lovastatin 10, 20, or 40 mg produced LDL-lowering within the range of –33% to –46% with an additional 13 to 15% reduction over lovastatin monotherapy.

Table 4. Mean Percent Change in LDL-C from Baseline in P00680 (Eze/Simvastatin Co-administration) Study

	Placebo n=70	EZ n=61	Simva 10 n=70	EZ + Simva 10 n=67	Simva 20 n=61	EZ + Simva 20 n=69	Simva 40 n=65	EZ + Simva 40 n=73	Simva 80 n=67	EZ + Simva 80 n=64
Baseline LDL, mg/dL	177.4	181.3	175.6	175.3	181.6	177.9	176.7	174.0	180.5	178.1
Mean % Chg from baseline (SEM)	-1.3 (1.7)	-18.1 (1.8)	-27.4 (1.7)	-44.4 (1.8)	-36.3 (1.8)	-44.8 (1.7)	-36.8 (1.8)	-53.5 (1.7)	-44.3 (1.8)	-56.3 (1.5)
Difference from same dose of statin-alone in mean % chg from baseline (95% CI)	NA	NA	NA	-17.0 (-21.8, -12.2)	NA	-8.5 (-13.5, -3.5)	NA	-17.2 (-22.0, -12.3)	NA	-12.6 (-17.6, -7.6)

In P00680, the co-administration of ezetimibe 10 mg to simvastatin 10, 20, 40, or 80 mg produced LDL-lowering within the range of –44 to –57% with an additional 8 to 17% reduction over simvastatin monotherapy.

Table 5. Mean Percent Change in LDL-C from Baseline in P00691 (Eze/Pravastatin Co-administration) Study

	Placebo n=65	EZ n=64	Prava 10 n=66	EZ + Prava 10 n=71	Prava 20 n=69	EZ + Prava 20 n=66	Prava 40 n=70	EZ + Prava 40 n=67
Baseline LDL, mg/dL	177.1	177.4	171.4	176.3	182.6	173.8	175.9	178.7
Mean % Chg from baseline (SEM)	+1.3 (1.6)	-18.7 (1.6)	-19.7 (1.6)	-34.1 (1.5)	-23.8 (1.5)	-38.0 (1.5)	-29.4 (1.5)	-41.1 (1.5)
Difference from same dose of statin-alone in mean % chg from baseline (95% CI)	NA	NA	NA	-14.4 (-18.6, -10.2)	NA	-14.2 (-18.4, -10)	NA	-11.7 (-15.9, -7.5)

In P00691, the co-administration of ezetimibe 10 mg to pravastatin 10, 20, or 40 mg produced LDL-lowering within the range of –34 to –41% with an additional 11 to 14% reduction over pravastatin monotherapy.

Table 6. Mean Percent Change in LDL-C from Baseline in P00692 (Eze/Atorvastatin Co-administration) Study

	Placebo n=60	EZ n=65	Atorva 10 n=60	EZ + Atorva 10 n=65	Atorva 20 n=60	EZ + Atorva 20 n=62	Atorva 40 n=66	EZ + Atorva 40 n=65	Atorva 80 n=62	EZ + Atorva 80 n=63
Baseline LDL, mg/dL	178.1	175.3	183.6	174.8	174.6	182.7	179.3	181.3	182.2	181.1

n % Chg from eline (SEM)	+5.9 (1.9)	-18.4 (1.9)	-35.5 (1.9)	-50.4 (1.9)	-39.8 (1.9)	-53.7 (1.9)	-43.1 (1.9)	-54.3 (1.9)	-51.4 (1.9)	-59.7 (1.9)
Difference from same dose of statin-alone in mean % chg from baseline (95% CI)	NA	NA	NA	-14.9 (-20.2,-9.7)	NA	-13.9 (-19.2,-8.6)	NA	-11.3 (-16.5,-6.1)	NA	-8.3 (-13.6,-3.1)

In P00692, the co-administration of ezetimibe 10 mg to atorvastatin 10, 20, 40 or 80 mg produced LDL-lowering within the range of –50 to –60% with an additional 8 to 15% reduction over atorvastatin monotherapy.

The sponsor also summarized the results of these trials by comparing the pooled LDL-lowering effects of ezetimibe and all doses of the individual statin versus the pooled results of all doses of the statin given alone. This analysis yielded similar findings to those summarized in Tables 3 through 6.

Although not presented in this secondary review, the effects of ezetimibe coadministered with a statin on total-C, TGs, HDL-C, and apoB were also evaluated as secondary efficacy measures. The effects of coadministration on total-C and apoB were consistent with that observed for LDL-C. For TGs and HDL-C, the mean (median for TG) percent changes from baseline was always in favor of coadministration; however, the difference in effect from the coadministration arm and the same dose of statin monotherapy was not consistently significant across the statin doses studied.

Similar to the presentation of data from the monotherapy trials, the summary of results from these 4 studies in the proposed label is by individual statins and doses studied and as pooled data across all doses of the individual statin. Calculated LDL-C measures were used instead of direct LDL-C but the differences in results were minor.

In addition to summarizing the lipid efficacy data, the sponsors inserted the following statement under the CLINICAL STUDIES section.

[ ]

Such a statement does not adequately summarize the efficacy of the full dosage range of two of the statins since the sponsor did not study pravastatin and lovastatin at their maximally approved doses (80 mg). Furthermore, the expected mean percent change in LDL-C from baseline at the lowest statin dose + EZ versus the highest tested statin dose is clearly depicted in the tables.

Effects on LDL-C with Ezetimibe Add-on Therapy to Ongoing Statin Use

In P02173, patients who have been on statin therapy for at least 6 weeks and whose LDL-C levels were at or above the NCEP-recommended target were enrolled in this trial with subjects randomized to receive either ezetimibe (n=390) or placebo (n=379). Approximately 40% of the cohort were receiving atorvastatin and 30% simvastatin at baseline. The remainder of the cohort was on the other marketed statins including cerivastatin as this study was conducted prior to its worldwide withdrawal. Overall, the two treatment groups appeared well-balanced with respect to type of background statin use.

The primary efficacy was the percent change from baseline to endpoint in calculated LDL-C within and between treatment groups. Secondary lipid efficacy measures included changes from baseline to endpoint in total-C, TG, and HDL-C. The results by treatment groups are summarized below:

Table 7. Lipid Changes in Add-On Study

	Statin + Placebo n=390	Statin + Ezetimibe n=379
Mean Baseline LDL-C, mg/dL	138.8	138.1
Mean Endpoint LDL-C, mg/dL	132.8	102.5
Mean % Chg from baseline	-3.7	-25.1
Mean Baseline Total-C, mg/dL	218.9	217.6
Mean Endpoint Total-C, mg/dL	212.7	179.1
Mean % Chg from baseline	-2.3	-17.1
Median Baseline TGs, mg/dL	137.0	136.0
Median Endpoint TGs, mg/dL	132.5	121.0
Median % Chg from baseline	-2.87	-13.9
Mean Baseline HDL-C, mg/dL	50.22	49.1
Mean Endpoint HDL-C, mg/dL	50.39	50.3
Mean % Chg from baseline	+0.99	+2.7

The addition of ezetimibe to ongoing statin therapy provided significantly greater lowering in LDL-C, total-C, and TG and greater increases in HDL-C. The sponsor also summarized the percent change in LDL-C between baseline and endpoint for simvastatin, atorvastatin, and other statin therapies in combination with placebo or ezetimibe. The results were similar to the pooled analysis summarized in the Table 7 with EZ + simva, EZ + atorv, EZ + other statin providing a difference in mean percent change from baseline compared to placebo of –24%, -21%, and –20%, respectively.

Two clinical scenarios by which ezetimibe might be used in combination with a statin were studied in this NDA. Patients on stable therapy with a statin who then received add-on ezetimibe therapy achieved a greater incremental reduction in LDL-C (up to –24%) than was observed when ezetimibe was concomitantly initiated with a statin (approximately –15% greater reduction over statin monotherapy). The results of these two treatment approaches suggest that greater LDL-lowering efficacy can be achieved if ezetimibe was added on to ongoing statin therapy. These results should be interpreted with caution, however, as the treatment differences may be secondary to different study designs and patient population.

Another secondary efficacy analysis in P02173 was to assess the proportion of patients not at NCEP ATP II LDL-C target levels at study entry on statin monotherapy who then achieved NCEP LDL-C target levels after the addition of ezetimibe to ongoing statin therapy. (*Note: This study was conducted prior to the updated NCEP ATP III guidelines being published. An exploratory analysis performed by the sponsor using NCEP ATP III target goals provided essentially similar results).* Not surprisingly, the greater LDL-lowering efficacy obtained with ezetimibe added to ongoing statin therapy allowed for more patients to achieve their NCEP target goals over continued statin monotherapy (72% vs. 19%, respectively).

Summarizing the [redacted] has recently been removed from labeling of several products. The ability to achieve a target LDL-C goal is dependent not only on the LDL-lowering efficacy of the product but is also dependent on the baseline LDL-C and CHD risk categories. For those individuals requiring minimal LDL reduction, a less potent LDL-lowering therapy is a reasonable choice of therapy whereas those with marked hypercholesterolemia and established heart disease requiring more aggressive therapy will likely warrant treatment with a more effective LDL-lowering therapy including combination treatment. The summary of efficacy in product labeling as mean percent reduction in LDL-C from baseline provides sufficient information to prescribers on what the expected LDL goal would be with the product. Describing efficacy as proportion of those achieving an LDL target goal will always favor the more potent LDL-lowering therapy but this "claim of superiority" in efficacy does not consider whether the more potent therapy is necessary nor does it factor in any safety concerns that may be associated with the more aggressive treatment.

In P02173, the majority of the patients were receiving mid-range or lower doses of statin therapy at the time of enrollment. From Table 15 of Clinical Study Report for Protocol 02173, only 20% and 19% of the simvastatin and atorvastatin groups, respectively, were receiving maximum approved doses. The highest approved dose of pravastatin (80 mg) was not evaluated in this protocol. In the clinical setting, individuals may achieve their NCEP target goal by maximizing treatment with the single agent. Consideration of combination therapy over monotherapy should include not only improved efficacy but whether the presumed safety of dose-sparing of one component (in this case, the statin) is not offset by the addition of a second agent (ezetimibe).

its inclusion in labeling should not be permitted.

Homozygous Familial Hypercholesterolemia
In Protocol 01030, 50 pediatric (11 yrs+) and adult patients with HoFH were treated initially with either simvastatin or atorvastatin 40 mg daily open-label in addition to diet and any other available therapies (e.g., LDL apheresis or bile acid sequestrants). At the end of this pre-randomization/statin lead-in period patients were randomized to one of the following 6 groups for 12 weeks:

- atorvastatin 80 mg (n=12)
- EZ + atorva 40 mg (n=12)
- EZ + atorva 80 mg (n=12)

- simvastatin 80 mg (n=5)
- EZ + simva 40 mg (n=4)
- EZ + simva 80 mg (n=5)

Primary efficacy analysis was percent change from endpoint to baseline in plasma concentrations of direct LDL-C between the pooled EZ 10 mg + statin 40/80 mg groups and the pooled statin 80 mg alone groups. The mean percent change from baseline in the EZ + statin 40/80 group was –20.7% compared to –6.7% in the statin 80 mg alone group. The difference between the two treatment groups was significant (p=.007). Comparisons between the two high doses of statin monotherapy to EZ + statin 80 mg therapy also showed a significant difference in mean percent changes in LDL-C favoring co-administration therapy (-7% for statin 80 mg vs –27.5% for EZ + statin 80 mg).

The following table summarizes the changes in LDL-C for the 6 individual treatment groups.

Table 8. Mean (25^{th}, 50^{th}, 75^{th}) percent changes from baseline at endpoint in direct LDL-C in HoFH patients by randomized treatment groups.

	atorva 80 n=12	EZ + atorva 40 n=12	EZ + atorva 80 n=12	simva 80 n=5	EZ + simva 40 n=4	EZ + simva 80 n=5
mean % chg from baseline	-3.5	-13.0	-24.7	-11.0	-12.0	-29.8
25^{th}	-10.1	-31.6	-35.8	-12.6	-20.1	-34.7
50^{th}	+0.4	-13.0	-21.2	-12.0	-5.5	-34.5
75^{th}	+3.0	+0.7	-16.3	-6.2	-3.9	-20.6
Concomitant apheresis, n (%)	6 (50%)	5 (41.7%)	6 (50%)	2 (40%)	3 (75%)	3 (60%)
Estimated LDL-Receptor Residual Activity						
< 5%	4	2	1	0	1	0
≥ 5%	2	2	4	0	0	0

Similar to the pooled analysis, the mean percent changes in LDL-C by individual treatments also indicate greater LDL-lowering when ezetimibe is added to high dose atorvastatin or simvastatin compared to statin monotherapy.

LDL-apheresis was a part of therapy in 25 patients. These individuals were maintained on a stable schedule of apheresis with efficacy determinations obtained before the apheresis session. The sponsor presented LDL-lowering efficacy by apheresis and non-apheresis groups. The effect of the ezetimibe + statin 40/80 mg group on LDL-lowering remained greater than the statin 80 mg group regardless of apheresis status. Interestingly, those patients in the EZ + statin group not receiving concurrent apheresis treatment had a greater mean percent reduction in LDL from baseline to endpoint than the EZ + statin group receiving apheresis. The higher baseline LDL-C in the non-apheresis group may have attributed to this treatment difference.

Table 9. LDL-lowering Efficacy by in Apheresis vs. Non-apheresis Patients		
	Apheresis	Non-apheresis

	Statin 80 mg	EZ + Statin 40/80 mg	Statin 80 mg	EZ + Statin 40/80 mg
Baseline mean LDL-C, mg/dL	323.83	279.7	365.44	364.9
Endpoint mean LDL-C, mg/dL	303.0	241.6	347.67	271.6
Mean % Chg from baseline (SEM)	-6.62 (2.3)	-12.6 (4.5)	-4.89 (5.1)	-27.2 (4.0)
Difference from Statin 80 mg in mean % chg from baseline (95% CI)	NA	-5.9 (-15.9, 4.0)	NA	-22.3 (-35.0, -9.7)

LDL-lowering efficacy was also presented for patients with a genotypic diagosis of HoFH which included those individuals with two identical mutant alleles or two non-identical mutant alleles for the LDL-receptor gene. Thirty-two out of the 50 patients randomized were identified as HoFH by genotyping (statin 80 n=12; EZ +statin 40/80 n=20). The mean percent change in LDL from baseline to endpoint was –18% in the EZ + statin 40/80 group versus –3.6% in the statin 80 mg group, similar to the findings for the entire cohort.

In the proposed label, the sponsor presented only LDL-C efficacy results in the following treatment group comparisons: statin 80 mg; EZ + statin 40/80 mg; and EZ + statin 80 mg. As discussed in Dr. Temeck's review, the efficacy of EZ + statin therapy on [redacted] in patients with HoFH should also be included in the drug label.

Homozygous Sitosterolemia

The effects of ezetimibe in 37 pediatric (10 yrs+) and adult patients with homozygous sitosterolemia were evaluated in an 8-wk double-blind, placebo-controlled study preceded by screening and single-blind placebo run-in phases. Patients were eligible to enroll regardless of current/past therapies including apheresis, bile-acid sequestrants, or ileal bypass surgery. In those individuals on bile-acid therapy, attempts were made to reduce the frequency of bile-acid sequestrant dosing to once a day or, if not medically appropriate, the dosing of the bile-acid therapy and ezetimibe was separated by several hours. One patient in the ezetimibe group was receiving apheresis during the trial and excluded from the data analysis.

The primary efficacy variable was the percent change in sitosterol between baseline and endpoint. Other secondary efficacy variables included percent changes in plasma campesterol and LDL-C levels. Effects of ezetimibe on sitosterol and campesterol were the only efficacy variables summarized in the proposed label. The following table summarizes the relevant findings from this study (P00243).

Table 10. Effects of treatment on Sitosterol Levels in P02243

	Placebo N=7	EZ n=29
Mean baseline sitosterol,	18.5	21.0

mg/dL		
Mean endpoint sitosterol, mg/dL	17.8	16.2
Mean % chg from baseline (95% CI)	+4.0 (-6.9, 14.8)	-21.0 (-26.7, -15.3)
Difference from Pbo in Mean % Chg from Baseline (95% CI)	-25.0 (-36.7, -13.2)	

Table 11. Effects of treatment on Campesterol Levels in P02243

	Placebo N=7	EZ n=29
Mean baseline campesterol, mg/dL	9.7	11.0
Mean endpoint campisterol, mg/dL	8.9	7.9
Mean % chg from baseline (95% CI)	+3.2 (-7.9, 14.3)	-24.3 (-30.2, -18.4)
Difference from Pbo in Mean % Chg from Baseline (95% CI)	-27.5 (-39.6, -15.4)	

The sponsor summarized the efficacy findings by different strata including presence or absence of concomitant bile acid sequestrant therapy. Although ezetimibe therapy was able to lower both plant sterols better than placebo regardless of bile acid sequestrant use, the degree of sitosterol- and campesterol-lowering associated with ezetimibe was diminished in those patients receiving bile salt therapy. The sponsor had made modifications to the dosing interval of these two products in the study protocol as a matter of precaution based on an *in vitro* study suggesting a potential for a pharmacokinetic interaction between the glucoronide metabolite of ezetimibe and bile salt sequestrants.

The product label does discuss the effects of concomitant administration of cholestyramine and ezetimibe under the *Drug Interactions* section of PRECAUTIONS; however, there is no recommendation to separate the dosing of these two class of drugs under DOSAGE AND ADMINISTRATION.

Efficacy of Ezetimibe by Gender, Race, and Age

As discussed in Section IX.B. of Dr. Temeck's review, the treatment effect of ezetimibe monotherapy and in combination with statins was consistent across the gender and age subgroups.

There were differences in the effect of ezetimibe treatment on LDL-C by race observed in comparative analyses between Caucasians and non-Caucasians and between

Caucasians and specific ethnic groups. The results for Caucasians versus non-Caucasians are summarized in the following tables. This reviewer does not summarize the non-Caucasian group by specific ethnicity as the sample size was too small to derive any meaningful data. The results for the Caucasian vs. non-Caucasian subgroups suggest an attenuated response in non-Caucasians to ezetimibe treatment for LDL-lowering. These results were not consistent across all trials and confounded by a greater placebo effect often seen in the non-Caucasian group. As a result of these differences and the small number of non-Caucasians, no conclusion can be made from these data other than that ezetimibe monotherapy and in combination with statins have not been adequately studied in non-Caucasians.

Table 12. Efficacy by Race in 2 Pbo-controlled Monotherapy trials

	N	Mean % Chg from Baseline	Difference from Placebo
P00474			
Caucasian			-18.3
Placebo	177	+0.2	
Ezetimibe	550	-18.1	
Noncaucasian			-19.2
Placebo	22	+1.4	
Ezetimibe	56	-17.8	
P00475			
Caucasian	195		-17.8
Placebo	568	+0.6	
Ezetimibe		-17.2	
Noncaucasian			-10.4
Placebo	15	-3.2	
Ezetimibe	60	-13.6	

Table 13. Mean Percent Change (SEM) in Plasma Concentration of Direct LDL-C Between baseline and Endpoint: Factorial Coadministration Studies-Subgroup Analysis (Intent-to-Treat Data Set)
From Dr. Jean Temeck's review of NDA 21-445

Race	N	All Statin	N	Ez + All Statin	[Ez + Statin] – [All Statin] 95% CI
Caucasian	807	-32.2 (0.6)	803	-46.9 (0.6)	-14.6 (-16.2, -13.0)
Non-Caucasian	120	-34.3 (1.6)	111	-40.9 (2.0)	-6.6 (-11.6, -1.6)

Safety Results

Dr. Bruce Stadel has thoroughly reviewed the original safety data and the updated safety reports submitted to this NDA. This secondary review will highlight only the number of patients and duration of exposure to drug therapy and the relevant safety findings from Dr. Stadel's review.

Reports on 4,584 patients exposed to ezetimibe were submitted to this NDA. The clinical data sources from which these reports were generated are summarized as follows (see Table 1 for description of individual Phase 2/3 and ongoing trials):

Table 14. Clinical Data Source for Safety Review

Clinical Trial Source	N	Duration of Treatment
32 Clinical Pharmacology Studies	552	varied from single dose to 2 weeks
12 Completed Phase 2/3 Studies	3350	8-12 weeks
4 Ongoing, Uncontrolled, Extension Studies	682	1-2 yrs*

*Safety data from these 4 extension studies were provided through the cut-off date 7-15-01

From the randomized controlled trials and the open-label extension studies in primary hypercholesterolemia, there were 1,341 patients who receivied ezetimibe treatment for at least 6 months and 1,018 patients who received therapy for at least 1 year.

Safety of Ezetimibe Monotherapy
Controlled safety data on ezetimibe monotherapy were available from 9 Phase 2/3 trials of 8 to 12 weeks duration involving 2,778 patients. Of this number, 795 were placebo-treated patients and 1983 received ezetimibe ——— mg as a daily monotherapy. Since the majority of ezetimibe treated patients received the 10 mg dose (1691/1983 = 85.3%) and the safety findings appeared similar between the All EZ dose groups and the 10 mg dose group, the summary of safety for ezetimibe in this review focuses only on the 10 mg dose. Dr. Stadel has provided the safety findings across all ezetimibe doses in the tables section of his review.

The following table summarizes the relevant clinical safety findings from Dr. Stadel's review of ezetimibe monotherapy.

Table 15. Summary of AEs in Monotherapy Pool

	Ezetimibe Monotherapy N=1691	Placebo N=795
Any AE	1061 (62.7%)	511 (64.3%)
serious	35 (2.1%)	19 (2.4%)
resulting in discontinuation	68 (4.0%)	30 (3.8%)
resulting in death	1 (0.06%)	0

from Tables 32 and 37 of Dr. Stadel's review

The incidenceof AEs, including serious, and the rate of discontinuation, was similar between ezetimibe monotherapy and placebo. The most common clinical AEs included upper respiratory tract infections, headaches, back pain, arthralgia, and musculoskeletal pain and the rates of these events were similar between the two treatment groups. AEs involving the liver and biliary system occurred in 32 (1.9%) of the ezetimibe group versus 11 (1.4%) in the placebo group. No cases of hepatitis or rhabdomyolysis occurred in these clinical trials.

Laboratory AEs of interest included liver functions test abnormalities and CK elevations. These results are summarized in the following table:

Table 16. LFTs and CK Findings in Monotherapy Pool

	EZ monotherapy N=1691	Placebo N=795

ALT and/or AST ≥ 3x ULN		
single occasion	14 (0.8%)	4 (0.5%)
consecutive	9 (0.5%)	3 (0.4%)
ALT and/or AST >5-10x ULN	2 (0.1%)	0
ALT and/or AST ≥ 10x ULN	0	0
CK ≥ 3x ULN	42 (2.5%)	11 (1.3%)
CK ≥ 10x ULN	4 (0.2%)	1 (0.1%)
CK elevations w/ symptoms		
≥ 5x ULN	4 (0.2%)	0
≥ 10x ULN	0	0

The incidence of single transaminase elevation ≥ 3x ULN was slightly higher in the EZ monotherapy group compared to placebo but the rate of consecutive elevations was similar between the two treatment groups and none of these exceeded 10x ULN. Similarly, the incidence of CK elevations ≥ 3x ULN was higher in the treatment versus placebo group but the rate of ≥ 10x ULN was similar across both treatment groups with none of these elevations associated with muscle symptoms.

Safety of EZ monotherapy by gender, race, and age

The following table derived from Dr. Stadel's review highlights several relevant safety findings by gender, race, and age.

Table 17. Safety Findings by Gender, Race and Age Category

	Ezetimibe Monotherapy	Placebo
AEs by Gender		
Females	599/880 (68.1%)	305/425 (71.8%)
Males	462/811 (57%)	206/370 (55.7%)
AEs by Race		
Caucasian	961/1523 (63.1%)	463/715 (64.8%)
non-Caucasian	100/168 (59.5%)	48/80 (60%)
AEs by Age Category		
< 65 yrs	706/1158 (61%)	356/548 (65%)
≥ 65 yrs	355/533 (66.6%)	155/247 (62.8%)
< 75 yrs	993/1593 (62.3%)	486/751 (64.7%)
≥ 75 yrs	68/98 (69.4%)	25/44 (56.8%)
ALT/AST ≥ 3x ULN		
Females	4/867 (0.5%)	4/420 (1%)
Males	10/807 (1.2%)	0/366 (0%)
CPK ≥ 3x ULN		
Females	5/867 (0.6%)	0/420
Males	37/807 (4.6%)	11/366 (3%)
Caucasian	23/722 (3.2%)	7/329 (2.1%)
Black	12/45 (26.7%)	4/19 (21.1%)
Other	2/40 (5.0%)	0/18

Within genders,, the incidence of AEs was similar between treatment groups. In females, the incidence of transaminase elevations was only 0.4% higher for ezetimibe compared to placebo; in males, the incidence was 1.2% higher. .

The incidence of AEs was similar for Caucasians and non-Caucasians, and between treatment groups in each racial group; however, this NDA database was predominantly comprised of Caucasians. Although a higher proportion of black males had CK elevations compared to other ethnic categories, these elevations were similar in the patients treated with ezetimbe and placebo.However, the small number ofblack male patients limits the conclusions that can be drawn fromthese data.

The incidence of AEs by age was similar between ezetimibe and placebo within the age categories: <65, ≥65, and <75 years. AEs were more frequent in ezetimibe-treated patients 75 years and older compared to placebo. As pointed out in Dr. Stadel's review, most of these AEs involved the musculoskeletal system including arthralgias, back pain, musculoskeletal pain, and others but there were no differences in the incidence of CK elevations by age category.

Safety of Ezetimibe Co-administered with a Statin

Data on the safety of ezetimibe coadministered with a statin were primarily derived from the pooling of 4 Phase 3 trials consisting of 259 placebo, 262 ezetimibe 10 mg monotherapy, 936 statin monotherapy, and 925 EZ + statin combination treated patients. Statin therapies included lovastatin (10, 20, 40 mg), simvastatin (10, 20, 40, 80 mg), pravastatin (10, 20, 40 mg), and atorvastatin (10, 20, 40, 80 mg). All these trials were 12 weeks in treatment duration.

The incidence of AEs, including serious, was similar across the different treatment groups: placebo, EZ monotherapy, statin monotherapy, and EZ + statin therapy. A safety finding of interest in the co-administration studies is whether the combined therapy would increase the risk of known adverse events associated with statin monotherapy. These included hepatic enzyme elevations and myopathy/CK elevations. The incidence of AEs in the Liver and Biliary System was similar between placebo and the ezetimibe monotherapy groups and progressively higher in the statin and EZ + statin groups, respectively. A similar pattern was also observed for laboratory AEs for transaminase levels.

Table 18. AEs in EZ/Statin Pool

	Placebo n=259	EZ monotherapy n=262	Statin monotherapy n=936	EZ + statin n=925
Any AE	166 (64.1%)	177 (67.6%)	606 (64.7%)	593 (64.1%)
serious	11 (4.2%)	7 (2.7%)	20 (2.1%)	22 (2.4%)
resulting in discontinuation	16 (6.2%)	13 (5%)	40 (4.3%)	53 (5.7%)
deaths	0	0	0	1 (0.11%)
AEs in the liver and biliary system	4 (1.5%)	5 (1.9%)	23 (2.5%)	53 (5.7%)
ALT/AST ≥ 3x ULN				
single	0	2 (0.8%)	9 (1%)	19 (2.1%)
consecutive	0	0	4 (0.4%)	13 (1.4%)

≥10x ULN	0	0	0	0
CK ≥ 3x ULN	3 (1.2%)	6 (2.4%)	25 (2.6%)	15 (1.6%)
CK > 5-10x ULN	0	3 (1.2%)	6 (0.6%)	4 (0.4%)
CK ≥ 10x ULN	0	0	4 (0.4%)	1 (0.1%)

The incidence of CK elevations was not increased with the combined use of ezetimibe and statins compared to the statin monotherapy group.

Safety of EZ + statin therapy by gender, race, and age
Across all treatment groups, females reported more AEs than males; however, the incidences of AEs of any intensity in femaleswere not markedly different across the treatment groups.

The incidence of ALT/AST and CK elevations in the EZ + statin group was higher in males than females. Similar to the EZ monotherapy safety review, a higher incidence of CK elevation was observed in black males over other ethnic groups. Again, the incidence was only slightly higher for ezetimibe compared to placebo, and the small number of patients in the black male category made it difficult to draw any firm conclusions None of these laboratory abnormalities resulted in a clinical adverse event.

Table 19. LFT and CK Results by Gender and Race

	Placebo	EZ monotherapy	Statin monotherapy	EZ + statin
ALT/AST > 3xULN				
Female	0/142	1/152 (0.7%)	7/539 (1.3%)	4/521 (0.8%)
Male	0/113	1/107 (0.9%)	2/390 (0.5%)	15/396 (3.8%)
CK > 3x ULN				
Female	0/142	2/152 (1.3%)	4/539 (0.7%)	3/521 (0.6%)
Male	3/113 (2.7%)	4/107 (3.7%)	21/390 (5.4%)	12/396 (3%)
Caucasian	2/98 (2.0%)	2/93 (2.2%)	15/343 (4.4%)	7/347 (2%)
Black	1/7 (14.3%)	2/4 (50%)	5/23 (21.7%)	3/16 (18.8%)
Other	0/8	0/10	1/24 (4.2%)	2/33 (6.1%)

The incidence of AEs in the EZ + statin group was similar across the different age categories: < 65 yrs (63.4%); ≥ 65 yrs (65.8%); < 75 yrs (63.7%); and ≥ 75 yrs (69.7%). These rates were also similar to placebo within the respective age categories (see Section 7.1.2.1.2.2 of Dr. Stadel's review; pg 98). Patients 75 years and older treated with ezetimibe monotherapy in this subset of the monotherapy pool database did experience a greater incidence of AEs (92.9%) compared to the patients treated with ezetimibe in the overall monotherapy pool database (69.4%). However, the number of patients making up this category within this database (n=44) was too small to make any definitive conclusions.

Uncontrolled extension studies of EZ monotherapy and EZ + statin therapy
There were no new or worsened adverse events or laboratory safety results identified in the extensions study results submitted in the 4- and 8-month safety updates.

Safety of Ezetimibe in HoFH and Homozygous Sitosterolemia
There were 50 and 37 patients enrolled in the HoFH and homozygous sitosterolemia trials, respectively. 45 patients in the HoFH study entered an ongoing, open-label extension study of 2 years duration. The safety of ezetimibe in these patient populations

was reviewed by Dr. Stadel and the results found to be similar to the safety in patients with primaryhypercholesterolemia.

CONCLUSIONS ON EFFICACY AND SAFETY OF EZETIMIBE

Ezetimibe (Zetia) was evaluated as monotherapy and combination therapy with statins in the treatment of primary hypercholesterolemia in 7 Phase 3 studies, as combination therapy with an approved statin for homozygous FH in one pivotal trial, and as adjunct to diet in homozygous sitosterolemia in one clinical study. Data from open-label extensions to several of these controlled trials were also submitted to this NDA.

In primary hypercholesterolemia, ezetimibe 10 mg monotherapy provides an average -18 to -19% reduction in LDL-C, -12 to -14% reduction in total-C, and -13 to -15% reduction in apo B lipoproteins from baseline that was significant from that observed with placebo. Triglyceride-lowering and HDL-raising were also observed with ezetimibe monotherapy; however, the results were variable across the different clinical studies.

The concomitant use of ezetimibe and statins provided incremental LDL-lowering over statin monotherapy in patients with primary hypercholesterolemia. Across all doses of statins studied, the concurrent administration of ezetimibe 10 mg and a statin provided an average additional reduction in LDL-C of –14% that was significant compared to the pooled statin monotherapy group. The addition of ezetimibe to on-going statin therapy provided an additional –20 to -24% reduction in LDL-C over the continued use of statin monotherapy. Significant reductions in total-C and apo B lipoproteins were also observed with the co-administration of ezetimibe and statins relative to statin monotherapy. Similar to the observations in the monotherapy studies, the concomitant use of ezetimibe and statins resulted in TG-lowering and HDL-raising; however, the results varied by study.

Patients with homozygous familial hypercholesterolemia treated with an approved statin for this condition had greater reductions in LDL-C when ezetimibe 10 mg was added to a regimen of either simvastatin or atorvastatin at 40 or 80 mg daily. An additional -14 to -18% reduction in LDL-C was observed compared to the statin monotherapy treatments.

Ezetimibe therapy in addition to conventional treatment for the rare disorder, homozygous sitosterolemia, resulted in significant reductions in the plant sterols, sitosterol (-25%) and campesterol (-28%) compared to placebo.

The safety of ezetimibe monotherapy and its combined use with statins was evaluated in controlled trials of maximum 3 months duration. Open-label extension studies provided additional safety data with the median duration of use for monotherapy and combination therapy being 18.5 months and 11.6 months, respectively. From a database comprised of 4,584 patients exposed to ezetimibe therapy there were no significant differences in the incidences of clinical adverse events, serious or resulting in discontinuation, between placebo and ezetimibe treatments. The addition of ezetimibe to statin therapy did result in higher frequencies of ALT and/or AST elevations compared to statin monotherapy, ezetimibe monotherapy, and placebo but none of these cases resulted in a clinical adverse event. The co-administration of ezetimibe and statin did not result in a greater frequency in CK elevation compared to statin monotherapy.

In conclusion, the sponsor has presented data supporting the effectiveness of ezetimibe therapies in the 3 proposed indications. In addition, the data support the conclusion that ezetimibe monotherapy and ezetimibe + statin therapy has an acceptable risk-benefit profile.

REGULATORY/ADMINISTRATIVE ISSUES

Financial Disclosure

These documents have been reviewed by Dr. Temeck and there was no evidence that ——————— investigators significantly impacted data integrity of this NDA.

Pediatric Studies

Pediatric studies involving children 10 years and older other than those involving patients with homozygous familial hypercholesterolemia or sitosterolemia have been deferred pending the review and approval of ezetimibe therapy in adults. A pediatric waiver for study children ≤ 10 years of age was granted in April 2001.

Phase 4 Studies

Both Drs. Temeck and Stadel have recommended a Phase 4 study be conducted to further evaluate ethnic difference in efficacy and safety. The non-Caucasian population comprised approximately 10% of the NDA cohort. The small number of non-Caucasian subjects within each treatment group limited any conclusion regarding the true effect of ezetimibe therapy in this patient subgroup. However, the efficacy results, although inconsistent from study to study, always trended towards an overall reduction in cholesterol. It is highly probable that with more patients studied, consistent results for LDL-lowering would also be observed in the non-Caucasian group. To the extent that this efficacy parameter can be monitored by prescribers through routine bloodwork, any absence or attenuation of efficacy can be detected and appropriately addressed.

A higher proportion of Black experienced CK elevations compared to the Caucasian patients. However, the incidence of CK elevation was similar between drug treatment and placebo groups within Blacks. This finding may represent ethnic differences in the normal distribution of CK levels.

Although the data in non-Caucasians are limited there is no evidence that ezetimibe is ineffective and unsafe in this subgroup of patients. A Phase 4 study is not recommended as a condition for approval of this application.

Proprietary Name

The proposed proprietary name, Zetia ®, was rejected by the Division of Medication Errors and Technical Support (DMETS). Recommendations to change the proprietary name due to concerns over sound-alike similarity to Zebeta ® were communicated to the sponsor by the Division in a letter dated July 8, 2002. .The sponsor submitted their response and arguments for maintaining the proposed proprietary name. Citing results of their marketing analyses, comparison of physical characteristics of the two drug products, and differences in packaging, the sponsor concluded that there was a low probability for medication errors between Zetia ® and Zebeta ®. A re-review of the DMETS consult, review of the sponsor's arguments, and discussions between the sponsor and Drs. Orloff and Parks subsequently led to the Division's decision to accept Zetia® as the proprietary name.

Study Audits

Manufacturing Facilities Inspections

Manufacturing facilities in Puerto Rico and Singapore were scheduled for inspection. The Puerto Rico site was issued a Withhold recommendation in February 2002 and upon re-inspection an acceptable recommendation was made. The Singapore facility is scheduled for inspection on October 15, 2002.

Clinical Audits

Two study sites were inspected and VAI (voluntary action indicated) letters were issued to both investigators, Drs. Dujovne and McGarry. The data submitted to this NDA were acceptable.

PROPOSED LABELING

The sponsor's proposed labeling has been reviewed and commented on by all disciplines. This reviewer has made comments on specific sections of the label in this review. Negotiations between the Division and the sponsor are scheduled with final labeling to be incorporated into the action package upon approval of this NDA.

RECOMMENDATIONS

Pending labeling negotiations and final recommendations on manufacturing facilities inspection this application should be approved.

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/s/

Mary Parks
10/15/02 04:04:39 PM
MEDICAL OFFICER

David Orloff
10/15/02 04:27:36 PM
MEDICAL OFFICER

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