CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

MEDICAL REVIEW(S)

AP 7·15·04

NDA 21-687
Vytorin

MEDICAL TEAM LEADER MEMO OF NDA

NDA #:	21-687
Drug Product Name:	Vytorin (fixed-dose combinations of ezetimibe/simvastatin 10/10, 10/20, 10/40, and 10/80 mg tablets)
Sponsor:	Merck Schering Plough
Type of Submission:	4S – Fixed Dose Combination Drug Product
Date of Submission:	September 24, 2003
Date Review Completed:	July 12, 2004

BACKGROUND AND INTRODUCTION

Vytorin® is a fixed-dose combination drug product of two approved lipid-altering drugs, ezetimibe (Zetia®) and simvastatin (Zocor®). Ezetimibe inhibits the intestinal absorption of cholesterol and was approved in 2002 for the treatment of primary hypercholesterolemia, both as monotherapy and in combination with statins. It is also approved for the treatment of hereditary sitosterolemia and in combination with atorvastatin or simvastatin for the treatment of homozygous familial hypercholesterolemia. Simvastatin is an HMG-CoA reductase inhibitor which blocks the rate-limiting enzyme in cholesterol synthesis. It has been marketed in the US since 1991 and has indications for the treatment of Types IIa, IIb, III, and IV dyslipidemia. In addition, clinical studies with simvastatin have demonstrated risk reductions for several cardiovascular clinical events, including CV mortality.

The lipid-altering efficacy and safety of co-administering ezetimibe and simvastatin have already been established in NDA 21-445 for Zetia®. In that application, the co-administration of ezetimibe 10 mg to simvastatin 10, 20, 40, or 80 mg produced LDL-lowering within a range of –44 to –57%, with an additional 8 to 17% reduction over simvastatin monotherapy.

This application now proposes to market the co-formulation of ezetimibe 10 mg and simvastatin as Vytorin 10/10, 10/20, 10/40, and 10/80 mg tablets. The basis of approval for such a product could have relied entirely on establishing bioequivalence between the fixed-dose combination tablet and its individual components co-administered; however, the applicant conducted additional lipid-altering efficacy studies to support the proposed label.

Proposed Labeling for Indications and Clinical Studies sections

The indications sought in this application are primary hypercholesterolemia (heterozygous familial and non-familial), mixed hyperlipidemia, and homozygous familial hypercholesterolemia (HoFH). The studies supporting these indication are described under the Clinical Studies section along with the results of studies evaluating Vytorin's efficacy in Type 2 diabetics, against atorvastatin, and at reaching NCEP ATP III LDL treatment goals.

Clinical Studies

Clinical studies submitted with this NDA focused on the effect of concurrent initiation of ezetimibe and simvastatin (Co-initiation Studies), the effect of adding ezetimibe to ongoing simvastatin therapy (Add-on Studies), and the effect of long-term treatment with the combination product (Long-term Studies). Some of these studies were submitted under NDA 21-445 for Zetia® and some are extension studies of base studies reviewed under the Zetia® application. Table 1 summarizes these clinical studies and indicates whether they were relied upon for labeling.

Table 1. Summary of Clinical Studies Reviewed in this Application

Protocol No.	Study Design	N	Treatment Groups	Results Included in Proposed Labeling
Co-Initiation Studies				
P005	12-week active treatments; factorial design	887	EZ = 92 Pbo = 93 All Simva = 349 EZ + All Simva = 353	Yes – Clinical Studies and Indications and Usage sections
P680 submitted under Zetia NDA	12-week active treatments; factorial design	668	EZ = 61 Pbo = 70 All Simva = 263 EZ + All Simva = 274	No – supportive of P005
P038	12-week active treatments; factorial design **Only clinical trial using the to-be-marketed product, Vytorin**	1,528	EZ = 148 Pbo = 146 All Simva = 612 EZ + All Simva = 604	No – submitted as Periodic Safety Update after initial submission of NDA
P023	23-week active treatments; titration-to-goal design	710	simva 20 mg start dose = 253 EZ + simva 10 mg start dose = 251 EZ + simva 20 mg start dose = 109 EZ + simva 40 mg start dose = 97	Yes – Clinical Studies section
P025	24-week active comparison w/ atorvastatin; force-titration design	788	atorva 10 mg start dose = 262 EZ + simva 10 mg start dose = 263 EZ + simva 20 mg start dose = 263	Yes – Clinical studies section
Add-On Studies				
P2173 submitted under Zetia NDA	8-week active treatment; EZ added to ongoing statin therapy	240	All simva = 117 EZ + All simva = 123	No
P700	14-week active treatments; addition of EZ to simva 20 mg vs. doubling simva 20 mg to 40 mg	100	All simva = 34 EZ 10 + simva 20 mg = 66	No
P021	24 week active treatments, addition of EZ to simva 20 mg vs. doubling simva 20 mg to 40 mg in Type 2 diabetics treated w/ thiazolidinediones	214	simva 40 mg = 110 EZ 10 mg + simva 20 mg = 104	Yes – Clinical studies section
Long-Term Extension Trials				
P0476	24-month, open-label,	1313	EZ monotherapy = 1012	No

Protocol No.	Study Design	N	Treatment Groups	Results Included in Proposed Labeling
	uncontrolled, safety and tolerability, extension study for P0474 and P0475 (base studies conducted under Zetia NDA)		EZ + simvastatin = 420 EZ + lovastatin = 192	
P2134	12-month, open-label, uncontrolled, safety and tolerability, extension study for P0679 and P0680 (base studies conducted under Zetia NDA)	359	EZ + simvastatin = 359	No
P005X1	48-week extension study of double-blind randomized treatment with EZ + simva (all doses)	768	simvastatin = 229 EZ + simvastatin = 539	Yes – Warnings
P2156	12-month extension study of P0680.	109	simvastatin = 22 EZ + simvastatin = 87	Yes - Warnings
P2173C	1 year extension to P2173	433	simvastatin = 78 EZ + simvastatin = 355	Yes - Warnings

In addition, a definitive bioequivalence study was conducted to bridge the preclinical and clinical data from the Zetia® NDA to this application. In this study the co-formulated tablets at 10/10 and 10/80 were bioequivalent to their respective components co-administered. This study (Protocol 039) and other biopharm studies are reviewed by the FDA's Office of Biopharmaceutics and Clinical Pharmacology.

CLINICAL EFFICACY RESULTS

Primary Hypercholesterolemia

Results from P005 and P680 were relied upon by the sponsor to support the following indication:

> *VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, ApoB, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia).*

P005 – A multi-center, double-blind, randomized, placebo-controlled, "factorial" design, 12-wk study to evaluate the efficacy of ezetimibe 10 mg/day coadministered with multiple doses of simvastatin in patients with primary hypercholesterolemia

After a 4-week screening and placebo run-in period, 887 patients with LDL-C ≥ 145 mg/dL and ≤ 250 mg/dL and TG ≤ 350 mg/dL were randomized to the following treatment groups:

- placebo (n=93)
- EZ 10 mg (n=92)

- Simvastatin 10 mg (n=81)
- EZ/Simvastatin 10 mg (n=87)
- Simvastatin 20 mg (n=90)
- EZ/Simvastatin 20 mg (n=86)
- Simvastatin 40 mg (n=91)
- EZ/Simvastatin 40 mg (n=89)
- Simvastatin 80 mg (n=87)
- EZ/Simvastatin 80 mg (n=91)

Baseline characteristics and lipid values were balanced across the treatment groups. Mean LDL-C values ranged between 173.9 and 176.1 mg/dL.

The primary efficacy endpoint was percent change from baseline at study endpoint in LDL-C. Analyses were performed on the pooled simvastatin and pooled EZ/simvastatin groups as well as by individual simvastatin dosing. The LS mean percent changes from baseline in LDL-C at study endpoint was –53.1% for the pooled EZ/simvastatin group versus –38.3% for the pooled simvastatin group. The difference between the pooled treatment groups was statistically significant ($p<0.001$). Similarly, results by individual treatment groups showed significantly greater LDL-lowering efficacy with the co-administration of EZ/simvastatin compared to the same simvastatin dose. The addition of ezetimibe to simvastatin 10 through 80 mg provided additional LDL-lowering over simvastatin monotherapy that ranged from –13.4% to –15.6%. Ezetimibe 10 mg monotherapy resulted in a mean reduction from baseline LDL-C of 20%. All combination EZ/simvastatin treatment groups provided more effective LDL-lowering than ezetimibe monotherapy.

The following table summarizes the efficacy results for selected lipoprotein variables in the pooled group and by individual dose of simvastatin.

Table 2. Summary of Lipid Results in Protocol 005

Treatment	N	LDL-C	Total-C	ApoB	HDL-C	TG	NonHDL-C
Pooled Data							
EZ + All Simva	353	-53	-38	-42	+8	-28	-49
All Simva	349	-38	-26	-29	+8	-15	-34
EZ 10 mg	92	-20	-14	-15	+7	-13	-19
Placebo	93	+3	+2	+3	+2	-2	+2
Ezetimibe + Simvastatin (by dose)							
EZ + Simva 10	87	-46	-32	-36	+9	-21	-41
EZ + Simva 20	86	-51	-37	-41	+8	-31	-47
EZ + Simva 40	89	-55	-39	-44	+9	-32	-51
EZ + Simva 80	91	-61	-43	-47	+6	-28	-55
Simvastatin (by dose)							
Simva 10	81	-31	-21	-23	+5	-4	-27
Simva 20	90	-35	-24	-25	+6	-14	-31
Simva 40	91	-42	-29	-33	+8	-19	-37
Simva 80	87	-46	-32	-35	+11	-26	-41

P680 – A phase 3, double-blind, efficacy and safety study of ezetimibe 10 mg in addition to simvastatin compared with placebo in subjects with primary hypercholesterolemia.

The results of this study were submitted and reviewed under NDA 21-445 for Zetia®. The duration of treatment, study design, entry criteria for LDL and TGs, and objectives of the study are identical to P005. The efficacy results for P680 are summarized in the following table.

Table 3. Summary of Lipid Results in Protocol 0680

Treatment	N	LDL-C	Total-C	ApoB	HDL-C	TG	NonHDL-C
			Pooled Data				
EZ + All Simva	274	-51	-37	-41	+9	-29	-47
All Simva	263	-37	-26	-30	+7	-20	-34
EZ 10 mg	61	-19	-13	-14	+5	-11	-17
Placebo	70	-1	-1	0	+1	+2	-1
			Ezetimibe + Simvastatin (by dose)				
EZ + Simva 10	67	-46	-33	-35	+9	-26	-42
EZ + Simva 20	69	-46	-33	-36	+9	-25	-42
EZ + Simva 40	73	-56	-40	-45	+11	-32	-51
EZ + Simva 80	65	-58	-41	-47	+8	-31	-53
			Simvastatin (by dose)				
Simva 10	70	-27	-18	-21	+8	-14	-25
Simva 20	61	-36	-26	-29	+6	-18	-34
Simva 40	65	-38	-27	-32	+6	-24	-35
Simva 80	67	-45	-32	-37	+8	-23	-41

P038 – A Multicenter, Randomized, Double-blind, Placebo-controlled, "Factorial" Design Study to Evaluate the Lipid-Altering Efficacy and Safety of Ezetimibe/simvastatin Combination Tablet In Patients with Primary Hypercholesterolemia

This is the <u>only</u> clinical efficacy study which used the to-be-marketed formulation of Vytorin. The study design, patient population, and treatment groups were identical to P005 and P680. The following table summarizes the efficacy findings for P038.

Table 4. Summary of Lipid Results in Protocol 038

Treatment	N	LDL-C	Total-C	ApoB	HDL-C	TG	NonHDL-C
			Pooled Data				
EZ + All Simva	604	-53	-37.6	-42.3	7 2	-24.3	-48 6
All Simva	612	-39	-27.7	-31.6	6.8	-20.8	-35.9
EZ 10 mg	148	-18 9	-13.3	-14.8	5.0	-10.7	-17.6
Placebo	146	-2.2	-1 4	-0.4	-0.3	-1.9	-1.6
			Ezetimibe + Simvastatin (by dose)				
EZ + Simva 10	151	-44.8	-31.4	-34 9	8.0	-22.5	-40.5
EZ + Simva 20	153	-51.9	-36.3	-41.1	9.8	-24.3	-47.4
EZ + Simva 40	146	-55.2	-39.2	-44.3	5.5	-22.9	-50.6
EZ + Simva 80	154	-60.2	-43.4	-48.8	5.6	-30.7	-55.7
			Simvastatin (by dose)				
Simva 10	155	-32.7	-23 1	-26.2	5.4	-17.1	-30 0
Simva 20	147	-34.2	-24.0	-27.7	7.4	-18.1	-31 7

Simva 40	154	-40.6	-28.9	-33.2	7.5	-21.2	-37.5
Simva 80	156	-48.5	-34.7	-39.4	7.1	-26.6	-44.5

In conclusion, all three studies demonstrated greater LDL-lowering efficacy with the combination of ezetimibe and simvastatin over either components individually.

Medical Officer's comment: Since P038 is the only efficacy study of the 3 trials that used the to-be-marketed Vytorin tablets, the results from this trial should be summarized in the Vytorin® labeling.

Pooled Analysis

To support an indication for the use of Vytorin® in patients with mixed hyperlipidemia the sponsor performed a pooled analysis of P005 and P680. Mixed hyperlipidemia refers to patients with elevations in both LDL-C and TGs. In both these studies, patients were eligible if LDL-C levels were between 145 and 250 mg/dL (inclusive) and if TG levels were ≤ 350 mg/dL. The pooled analysis selected the subgroup of patients with TG levels > 200 mg/dL. Out of 1,555 patients in both studies, 490 patients met the TG criterion of > 200 mg/dL. Baseline characteristics of these patients were similar across the 4 treatment groups analyzed (placebo, EZ 10 mg, All Simva, EZ 10 mg + All Simva).

The combination of ezetimibe and simvastatin (across all doses of simva) significantly reduced LDL-C, TC, and TGs compared to simvastatin monotherapy (across all doses) in patients with TG > 200 mg/dL and ≤ 200 mg/dL. The following table summarizes the results for LDL and TGs in the patients with hypertriglyceridemia.

Table 5. Lipid Results in Patients w/ Mixed Dyslipidemia (Pooled Analysis of P005 and P680)

	Placebo N=45	EZ 10 mg N=55	All Simva N=178	EZ + All Simva N=207
LDL-C				
Mean Baseline (SD)	182.8 (27.7)	180.3 (24.0)	179.3 (23.4)	178.0 (26.8)
Mean Endpoint (SD)	181.2 (31.7)	149.4 (24.3)	108.5 (26.3)	83.9 (29.6)
LS Mean% Chg from bsl	-0.7 (-4.6, +3.3)	-16.7 (-20.3, -13.1)	-38.6 (-40.7, -36.6)	-52.9 (-54.8, -51.1)
Diff b/w EZ + Simva and All Simva				
LS Mean				-14.3 (-17, -11.5)
p-value				<0.001
Total-C				
Mean Baseline (SD)	278.3 (28.6)	275.5 (30.2)	274.9 (26.9)	273.2 (29.7)
Mean Endpoint (SD)	275.8 (33.9)	240.0 (29.9)	197.1 (31.7)	169.4 (37.4)
LS Mean % Chg from bsl	-0.7 (-3.8, 2.4)	-12.6 (-15.4, -9.8)	-27.7 (-29 2, -26.1)	-38.0 (-39 4, -36.5)
Diff b/w EZ + Simva and All Simva				
LS Mean				-10 3 (-12.4, -8.2)
p-value				<0.001
HDL-C				
Median Baseline (SD)	44.0 (9.3)	42 0 (12.6)	44.3 (12.2)	43 3 (10.7)
Median Endpoint (SD)	46.0 (7.4)	48.0 (15.8)	48.0 (13.0)	49.0 (13.0)
LS Mean % Chg from bsl	3.7 (-0.4, 7.7)	8.3 (4.9, 11 7)	10.6 (8.4, 12.7)	11.1 (9.1, 13.2)

Diff b/w EZ + Simva and All Simva				NS
TG				
Median Baseline (SD)	251.0 (36.0)	243.0 (53.0)	246.0 (54.9)	248.0 (58.9)
Median Endpoint (SD)	232.0 (79.1)	203.0 (94.9)	186.5 (70.7)	161.0 (65.1)
LS Mean % Chg from bsl	-8.9 (-14.8, -3.1)	-19.7 (-26.5, -12.9)	-25.6 (-29.3, -22.0)	-34.7 (-38.0, -31.4)
Diff b/w EZ + Simva and All Simva				
LS Mean				-34.7 (-38.0, -31.4)
p-value				<0.001

Homozygous Familial Hypercholesterolemia

Ezetimibe in combination with atorvastatin or simvastatin for the treatment of homozygous familial hypercholesterolemia (HoFH) was evaluated under P1030 under the Zetia® NDA. In this 12-week, double-blind study, 50 HoFH patients receiving atorvastatin 40 mg or simvastatin 40 mg in an open-label, lead-in period were randomized to one of 6 treatment groups: atorva 80, EZ/atorva 40, EZ/atorva 80, simva 80, EZ/simva 40, or EZ/simva 80. This study demonstrated greater LDL-lowering in HoFH patients who had ezetimibe added to their statin treatment than increasing the statin dose.

MSP has submitted the data for only the simvastatin and EZ/simvastatin patients in P1030. There were 9 patients who received EZ + simvastatin (40 or 80 mg) and 5 patients who received simvastatin 80 mg monotherapy during the 12-week, double-blind treatment phase.

EZ + simvastatin 40 or 80 mg (pooled) reduced LDL-C by 23% from the simvastatin 40 mg alone baseline compared to a 13% reduction achieved with increasing the simvastatin dose to 80 mg alone. The EZ + simvastatin 80 mg group (n=5) achieved an average 29% further reduction in LDL-C from baseline.

The proposed indication for HoFH in the Vytorin label is as follows:

> *Vytorin is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.*

Medical Officer's comments: This proposal is acceptable. This indication has already been approved in the Zetia® label based on data from the same study submitted to this NDA. In addition, the proposal to summarize descriptive statistical results from this study under the Clinical Studies subsection of CLINICAL PHARMACOLOGY is acceptable.

Attaining NCEP Treatment Goals

Results from P023 are relied upon to support a change to the Clinical Studies subsection of CLINICAL PHARMACOLOGY. This study was a 23-week, double-blind, controlled study in 710 patients with CHD or CHD risk equivalents who had LDL-C ≥ 130 mg/dL. Patients were randomized to 4 treatment groups: EZ/simvastatin 10, EZ/simvastatin 20, EZ/simvastatin 40, or simvastatin 20 mg. The LDL-C treatment goal for these patients

(based on NCEP ATP III Guidelines) is < 100 mg/dL. Patients not achieving this goal had their simvastatin dose titrated at 6-week intervals to the maximum dose of 80 mg.

At the end of 6 weeks, 45.5% of the simvastatin 20 mg group achieved an LDL-C < 100 mg/dL. In the combination EZ/simvastatin (10, 20, and 40 mg) groups, 74.8%, 83.3%, and 87.5% achieved the same LDL target goal. At the end of study, after necessary up-titration to meet treatment goals, the simvastatin monotherapy group achieved LDL-C < 100 mg/dL in 59.3% of the patients. The combination EZ/simvastatin groups did not change much with 77.6%, 82.6%, and 85.6% at treatment goal by the end of study.

More patients in the simvastatin monotherapy group required increases in their simvastatin dose to achieve NCEP goals compared to the combination EZ/simvastatin groups.

These results are not unexpected as the sponsor has already demonstrated in several studies that the addition of ezetimibe to simvastatin provides for greater LDL-lowering than the same dose of simvastatin alone.

The following table summarizes the mean percent changes in LDL-C from baseline after 6 weeks in the P023 study. These results are similar to results in P005 and P680.

Table 6. Summary of Lipid Results in P023

	Simva 20 mg	EZ/Simva 10	EZ/Simva 20	EZ/Simva 40
N	253	251	109	97
mean % chg in LDL	-38	-47	-53	-59

Medical Officer's Comments: This reviewer does not recommend the inclusion of these results in the package insert. A summary of percentage of patients reaching NCEP goals is not clinically relevant to individual prescribing decisions. These decisions should be based on a patient's baseline lipid profile, cardiac risk profile, and other factors that may also impact the choice of lipid-altering drugs. The essential information to be conveyed is the average expected change in LDL-C by treatment regimen and/or dose. The fact that combination ezetimibe and simvastatin treatment provides greater LDL-lowering than simvastatin monotherapy is certainly not obscured in the proposed package insert. From this information alone, it is self-evident that an individual would more likely achieve an LDL goal with the combination therapy over the monotherapy.

Comparative Efficacy with Atorvastatin

The results from P025 are summarized under the Clinical Studies subsection of CLINICAL PHARMACOLOGY in the proposed package insert for Vytorin®. This was a 28-week, double-blind, randomized, forced-titration study comparing ezetimibe/simvastatin to atorvastatin in patients not at NCEP ATP III treatment goals for their CHD risk category. Patients also had to have had a serum TG ≤ 350 mg/dL. They were stratified according to LDL-C levels of ≥ 130 mg/dL and < 160 mg/dL, ≥ 160 mg/dL and < 190 mg/dL, and ≥ 190 mg/dL, then randomized 1:1:1 to the following dosing groups:

- EZE/simvastatin 10 mg start dose
- EZE/simvastatin 20 mg start dose

- atorvastatin 10 mg start dose

Patients had their statin dose increased by 6 week intervals as follows:

Table 7. Dose Titration Scheme for P025

Period 1 (Weeks 1 to 6)	Period 2 (Weeks 7 to 12)	Period 3 (Weeks 13 to 18)	Period 4 (Weeks 19 to 24)
Atorvastatin 10 mg	Atorvastatin 20 mg	Atorvastatin 40 mg	Atorvastatin 80 mg
EZ/Simva 10 mg	EZ/Simva 20 mg	EZ/Simva 40 mg	EZ/Simva 80 mg
EZ/Simva 20 mg	EZ/Simva 40 mg	EZ/Simva 40 mg	EZ/Simva 80 mg

The primary endpoint was the percent change from baseline in LDL-C after the first 6 wk period (i.e., comparisons of atorva 10 mg vs EZ/Simva 10 mg vs EZ/Simva 20 mg). Secondary efficacy measures included comparison of lipid-altering efficacy at the end of other study periods.

EZ/simvastatin 10 and 20 mg were more effective at lowering LDL-C, Total-C, ApoB, and Non-HDL-C, and raising HDL-C than atorvastatin 10 mg at the end of the first period (Week 6). In addition, the combination of EZ/simvastatin was a more effective regimen than atorvastatin for most parameters measured within a specified study period. The reductions in TG, however, were not significantly different between the atorvastatin and EZ/simvastatin groups.

Table 8. Summary of Lipid Results in P025

	LDLC	TC	ApoB	HDLC	TG	NonHDLC
Week 6 – Period 1						
Atorva 10 EZ/Simva 10 EZ/Simva 20	-37 -46* -50*	-28 -34* -36*	-32 -38* -41*	+5 +8* +10*	-23 -26 -25	-35 -43* -46*
Week 12 – Period 2						
Atorva 20 EZ/Simva 20 EZ/Simv 40	-44 -50* -54*	-33 -37* -39*	-38 -41* -45*	+7 +9 +12*	-28 -28 -31	-42 -46* -50*
Week 18 – Period 3						
Atorva 40 EZ/Simva 40	-49 -56*	-37 -40*	-42 -45*	+8 +11*	-31 -32	-47 -52*
Week 24 – Period 4						
Atorva 80 EZ/Simva 80	-53 -59*	-40 -43*	-45 -49*	+6 +12*	-35 -35	-50 -55*

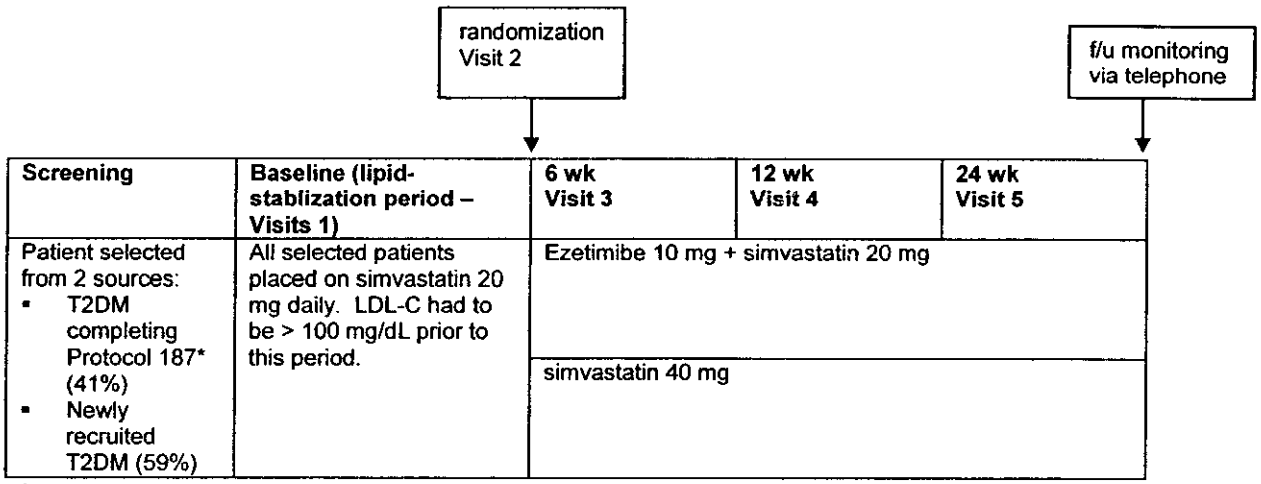
*p≤0.05 for difference w/ atorvastatin in the specified period

Efficacy in Type 2 Diabetics

Results from P021 are summarized in the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section of the proposed package insert. The objective of this trial was to evaluate the efficacy and safety of ezetimibe plus simvastatin versus simvastatin monotherapy in Type 2 diabetics treated with a stable dose of a thiazolidinedione for 3 months prior to study entry. Two hundred and fourteen patients were enrolled in this 24-week, randomized, double-blind study. Patients were selected from 2 sources:

1. Type 2 diabetics who were enrolled in and completed another Merck study (Protocol 187). This was a 24-week, double-blind study evaluating the efficacy and safety of simvastatin 40 mg to placebo in TZD-treated patients. These patients are referred to as "rollover patients" and comprised 41% of P021 cohort.
2. Newly recruited Type 2 diabetics on a stable dose of TZD for 3 months who had an LDL-C > 100 mg/dL. These patients comprised 59% of the P021 cohort.

Both these patient groups were entered into a lipid-stabilization period where they received simvastatin 20 mg daily open-label. After this initial stabilization period, patients were randomized to either an additional dose of simvastatin 20 mg (total daily dose = 40 mg) or to ezetimibe 10 mg daily.



*This study investigated the efficacy and safety of simvastatin 40 mg compared to placebo in TZD-treated T2DM patients

To achieve balance in thiazolidinedione use, patients were also stratified according to whether they were treated with pioglitazone or rosiglitazone. Within each stratum, patients were further stratified by TZD dose although it was possible that TZD doses were titrated for glycemic control.

The *primary endpoint* was the percent change from baseline in LDL-C based upon the average of Week 6, 12, and 24 measurements. Baseline LDL-C measurement reflected lipid levels achieved after a minimum 6-week treatment with simvastatin 20 mg (Visit 2, Day 1 predose).

Patients in both treatment groups were balanced for most baseline characteristics and laboratory measures including gender, age, sex, lipid profile, and glycemic control. Baseline mean LDL-C was 91.4 and 93.7 mg/dL in the simvastatin 40 and EZ/simvastatin 20 mg groups, respectively. Mean HbA1c was 7.3% in both treatment

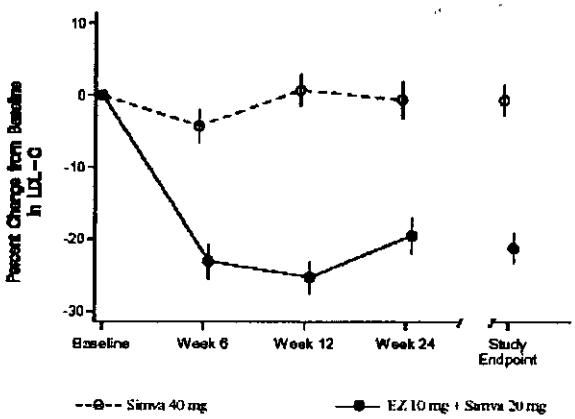
groups. Other anti-diabetic drugs were allowed during the study and there was no obvious imbalance between the 2 treatment groups (reference Table 15 of sponsor Clinical Study Report for P021).

Compliance was summarized by the following categories: > 95%, 95-90%, 90-85%, 85-75%, 75-60%, and < 60%. Compliance at > 95% was higher in the eze/simva 20 mg group (81.7%) compared to simva 40 mg group (70%). Conversely, compliance at < 60% was higher in the simva 40 mg group (8.2%) versus the eze/simva 20 mg group (2.9%). The per-protocol analysis excluded patients with compliance < 75% (9 in simva 40 group and 5 in EZ/simva group).

Based on the modified intention-to-treat approach, the addition of ezetimibe 10 mg to simvastatin 20 mg lowered LDL-C more significantly than doubling the dose of simvastatin from 20 to 40 mg (LS means: -20.8% vs. –0.3%, p<0.001). Study endpoint was an average of 3 measures at 3 different timeperiods (wks 6, 12, and 24). Figure 3 obtained from sponsor's submission depicts the percent change from baseline at Visits 3, 4, and 5 in both treatment groups.

Figure 3

Plot of LS Mean Percent Change From Baseline (±SE) in LDL-C
Over Time and at Study Endpoint[1]
Modified Intention-to-Treat Approach



[1] Average of Week 6, 12, and 24 measurements

While it was expected that EZ/simvastatin 20 mg would achieve greater LDL-lowering than simvastatin 40 mg based on previously conducted studies, it was surprising that the simvastatin group showed no further incremental reduction in LDL-C when the dose was doubled from 20 mg to 40 mg. Historically, a doubling of a statin dose achieves a 4 to

6% further reduction in LDL-C levels. Discussions with the sponsor raised several possible explanations including the patient population, the concurrent use of TZDs, and a baseline LDL-C that is lower than average (mean 90.8 mg/dL). A notable finding was that the distribution of LDL-C at endpoint was highly skewed. A non-parametric analysis performed by both the sponsor and the FDA statistician still confirmed the statistical difference between the treatment groups; however, this type of analysis better reflected the expected response of the simvastatin monotherapy group.

Table 9. % change in LDL-C from baseline at endpoint (from Dr. Todd Sahlroot's review, Table 1)

% change in LDL-C from baseline	Simva 20 + ezetimibe n=103	Simva 40 N=107	Treatment difference
Baseline mean	92.8 mg/dL	90.8 mg/dL	
Mean % chg	-21.2	-0.6	-20.6
Adjusted mean (SE)	-20.8 (2.2)	-0.3 (2.2)	-20.5
Median %	-24.7	-4.9	-19.8
Range (min, max)	-55.4, +111.3	-30.6, +56.4	

Medical Officer's Comments : This reviewer recommends the results of the non-parametric analysis be used in describing the results of this study in the label. Although this was not the primary analysis specified in the protocol, the highly variable and skewed distribution of response justifies its use over the traditional parametric analysis.

CLINICAL SAFETY

Simvastatin 5 to 40 mg was approved in 1991, and the 80 mg dose was approved in 1998. Its safety has been extensively studied in clinical trials including two 5-year, placebo-controlled clinical trials involving approximately 12,000 patients. The most serious safety concern associated with simvastatin and other statin therapies is myopathy with a potential for development of rhabdomyolysis with or without renal failure.

Ezetimibe was approved in 2002 based on a clinical development program that included data from more than 4,500 patients exposed to ezetimibe. The safety review revealed a slightly higher increase in liver transaminases in the ezetimibe group compared to placebo but no cases of hepatitis were reported. Clinical adverse events were more commonly reported in the hepato-biliary body system. Recent post-marketing reports for ezetimibe have included reports of anaphylaxis-like side-effects and pancreatitis. Ezetimibe was associated with increased bile-cholesterol content in preclinical studies; however, it is unclear whether these findings result in an increased risk for developing pancreatitis. Gallbladder-related AEs were selectively reported and these findings are summarized below.

There were four, placebo-controlled, 12-week, Phase 3 clinical studies reviewed under the Zetia® NDA that included safety data for the co-administration of ezetimibe and a statin (lovastatin, simvastatin, atorvastatin, and pravastatin). The following table summarizes the pertinent safety findings from the review of those 4 studies:

Table 10. AEs in EZ/Statin Pool (obtained from review of NDA 21-445)				
	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%)

While the incidence of AEs, including serious ones, was similar across the different treatment groups, there was a progressive increased incidence of AEs in the Liver and Biliary System in the statin monotherapy (2.5%) and EZ+statin (5.7%) groups compared to EZ monotherapy and placebo. A similar finding was also observed for liver transaminase elevations.

The safety of ezetimibe and simvastatin has been evaluated in over 3200 patients in this application, including data from 5 long-term extension studies ranging from 48 weeks to 24 months. Three of these studies were double-blind, controlled studies comparing simvastatin monotherapy to EZ + simvastatin (P005X, P2156, and P2173C).

This memo will summarize the safety findings of each of these 3 long-term extension studies with a focus on incidence of muscle and liver adverse events.

P005X

Patients completing the base study, P005 (see efficacy section) were eligible for this 48 week extension study provided their LDL-C was > 50 mg/dL, CK level was < 5x ULN, and ALT/AST values were < 3x ULN. Patients received 1 of 7 blinded study treatments:

1. Eze + simva 10 (n=134)
2. Eze + simva 20 (n=135)
3. Eze + simva 40 (n=129)
4. Eze + simva 80 (n=141)
5. Simva 20 (n=79)
6. Simva 40 (n=77)
7. Simva 80 (n=73)

Patients taking placebo, eze 10 mg, or simva 10 mg during the base study period were switched to one of the 4 eze + simva co-administration groups. All other patients remained in their assigned treatment groups. The mean number of days on co-administration therapy (all simva doses) was 278.8 days. Pooled simvastatin therapy was administered for a mean of 305.6 days.

A total of 768 patients entered the extension study; 229 received simvastatin (20, 40, or 80 mg) and 539 received eze + simvastatin (10, 20, 40, or 80 mg). The overall disposition of these patients is summarized in the following table obtained from the sponsor's CSR:

Overall Disposition of Patients by Pooled Treatment Groups

Time Frame	All Simva[†] (N=229)	EZ 10 mg + All Simva[‡] (N=539)	Total
Treatment (Ext1)	n=229	n=539	768
Patient completed	203 (88.6%)	414 (76.8%)	617
Patient discontinued:	26 (11.4%)	125 (23.2%)	151
Clinical adverse experience	6 (2.6%)	25[§] (4.6%)	31
Laboratory adverse experience	2 (0.9%)	16 (3.0%)	18
Lack of efficacy	1 (0.4%)	0 (0.0%)	1
Lost to follow-up	3 (1.3%)	4 (0.7%)	7
Patient discontinued for other	1 (0.4%)	44 (8.2%)	45
Patient moved	0 (0.0%)	2 (0.4%)	2
Patient withdrew consent	13 (5.7%)	32 (5.9%)	45
Protocol deviation	0 (0.0%)	2 (0.4%)	2

[†] Pool of all doses of simvastatin.
[‡] Pool of all doses of simvastatin coadministered with ezetimibe 10 mg.
[§] In the Overall Disposition of Patients table, patients who discontinued due to clinical adverse experiences are counted based on the visit of their discontinuation status. In the Clinical Adverse Experience Summary table, patient are counted based on the visit of the adverse experience resulting in the discontinuation. Because of this, one patient (AN 7583), who had a clinical adverse experience that began at a visit in the base study, but did not discontinue until a visit in the extension study, is counted here in the Overall Disposition of Patients table but not in the Clinical Adverse Experience Summary table (Table 51 and Table 52).

The most common reason for discontinuation was listed as "other"; however, these were patients who had 2 consecutive LDL-C < 50 mg/dL with 44 out 45 patients assigned treatment with combination therapy. Thirty-one of these patients were on eze + simva 80 mg daily treatment.

Discontinuations due to clinical AEs occurred more frequently in the co-administration group (4.6% vs 2.6%). Likewise, the incidence of laboratory AEs resulting in study discontinuation was higher in the co-administration group than simvastatin monotherapy (3.0% vs 0.9%). The following table summarize the overall incidences of clinical AEs.

APPEARS THIS WAY
ON ORIGINAL

Clinical Adverse Experience Summary by Pooled Treatment Groups

	All Simva[†] (N=229)		EZ 10 mg + All Simva[‡] (N=539)	
	n	(%)	n	(%)
Number (%) of patients.				
With one or more adverse experiences	159	(69.4)	393	(72.9)
With no adverse experience	70	(30.6)	146	(27.1)
With drug-related adverse experiences[§]	26	(11.4)	73	(13.5)
With serious adverse experiences	6	(2.6)	28	(5.2)
With serious drug-related adverse experiences	0	(0.0)	1	(0.2)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	6	(2.6)	24[¶]	(4.5)
Discontinued due to drug-related adverse experiences	5	(2.2)	15	(2.8)
Discontinued due to serious adverse experiences	1	(0.4)	6	(1.1)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	1	(0.2)

† Pool of all doses of simvastatin.
‡ Pool of all doses of simvastatin coadministered with ezetimibe 10 mg.
§ Determined by the investigator to be possibly, probably, or definitely drug related.
¶ In the Overall Disposition of Patient table (Table 6), patients who discontinue due to clinical adverse experiences are counted based on the visit of their discontinuation status. In the Clinical Adverse Experience Summary table, patients are counted based on the visit of the adverse experience resulting in the discontinuation. Because of this, one patient (AN 7583), who had a clinical adverse experience that began at a visit in the base study, but did not discontinue until a visit in the extension study, is counted in the Overall Disposition of Patients table but not here in the Clinical Adverse Experience Summary table.

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

The incidences of AEs were higher in the co-administration group compared to simvastatin monotherapy for the majority of subclassifications. A review of clinical AEs by body systems revealed that the most common AEs occurred in the following categories: Musculoskeletal and Connective Tissue Disorders; Infections and Infestations; and Gastrointestinal Disorders (all these occurred at rates> 20%). Closer evaluation of the specific AEs within each category did not reveal any marked differences in event rates that could be considered clinically relevant. Of note, the incidence of myalgias was 3.1% in the all simvastatin group versus 2.8% in the co-administration group.

Serious AEs occurred at a higher rate in the co-administration group than simva monotherapy group. There were *no deaths* in this study. The most common serious AEs occurred in the Gastrointestinal Disorder and Neoplasms Benign, Malignant, and Unspecified categories. The incidence of SAE was higher in the latter category where 1 patient in simvastatin a neoplasm (breast ca NOS) vs 6 in the co-administration group. Tumors diagnosed in this group included 1 basal cell ca, 1 breast ca nos, 1 lung cancer, 2 prostate cancers, and 1 transitional cell carcinoma. The number of events is too small to make any accurate conclusions on the drug-associated risks.

Notable laboratory AEs for simvastatin and ezetimibe include CK and liver transaminase elevations. There were no cases of myopathy or rhabdomyolysis; one patient had CK

elevations > 10x ULN [redacted]) but remained asymptomatic. He completed the study without incident and the laboratory abnormality was attributed to a history of "excessive fitness training".

While no cases of hepatitis or other clinical hepatic AEs were reported in this study, the incidence of consecutive > 3x ULN for ALT and/or AST levels was significantly higher in the co-administration group versus the simvastatin monotherapy group (15/530, 2.8% vs 1/227, 0.4%; p=0.049). There appears to be a dose relationship in the co-administration group as summarized in the following table:

Table 11. Incidence of Transaminase Elevations in P005X

	Simva Monotherapy			Co-Administration			
	Simva 20	Simva 40	Simva 80	EZ/Simva 10	EZ/Simva 20	EZ/Simva 40	EZ/Simva 80
ALT ≥ 3x ULN	0	0	1.4%	0.7%	0.8%	3.9%	5.8%
AST ≥ 3x ULN	0	0	0	0.7%	0	1.6%	4.4%
ALT and/or ALT ≥ 3x ULN	0	0	1.4%	0.7%	0.8%	3.9%	5.8%

Protocol 2156

Patients completing the base study, P0680 (reviewed under Zetia® NDA), were eligible for this 12-month extension study. Patients in the base study were from one of 10 different treatment groups: placebo, eze 10, eze + simva (10, 20, 40, or 80 mg), and simva (10, 20, 40, or 80 mg). Treatment assignment in the extension study was as follows:

Table 12.

Base Study		**Extension Study**
Placebo	→	Simva 10 mg daily
Eze monotherapy Eze + simvastatin	→	Eze + Simva 10 mg daily
Simva monotherapy	→	Eze or placebo (3:1 randomization) plus simvastatin 10 mg daily

A total of 109 patients enrolled in this extension study; 22 were assigned to simvastatin monotherapy and 87 were assigned to eze + simvastatin. Disposition of these subjects is summarized in the following table obtained from the sponsor's CSR for Protocol 2156. During the extension study period, at specified study visits, the simvastatin dose could be increased up to a maximum of 80 mg/day if NCEP ATP II target goals were not met. Few patients in the co-administration group required this upward titration; only 6 out of 87 patients required an upward titration to simvastatin 20 mg. There were no patients

exposed to eze + simva 40 or 80 mg in this extension period. Hence, safety information from this database is limited for the higher doses of Vytorin. In the simvastatin monotherapy group, 6 out of 22 patients required upward titration; two required simvastatin 20 mg and 4 required simvastatin 80 mg.

Disposition of Subjects	Simvastatin (n=22)	EZ 10 mg + Simvastatin (n=87)
Completed Study	18 (82)	66 (76)
Discontinued Study	4 (18)	21 (24)
Adverse Event	0	7 (8)
Lost to Follow-Up	0	4 (5)
Subject Did Not Wish to Continue	1 (5)	4 (5)
Noncompliance with Protocol	2 (9)	4 (5)
Administrative	1 (5)	2 (2)

Simvastatin = all doses of simvastatin; EZ 10 mg + Simvastatin = all doses of simvastatin coadministered with ezetimibe 10 mg.

The sponsor's safety analysis combined data from the co-administration groups in the base study, P680, with this extension study for a combined dataset from 241 subjects. The majority of these patients (142/241, 59%) received therapy for < 3 months, and 47/241 (20%) received co-administration therapy for ≥ 12 months. The mean extent of exposure on co-administration was 5.7 months.

The following table summarizes overall rates of Adverse Events and the individual categories of AEs.

Table 13.

	Simvastatin N=22	Ez + Simva N=87
Any AE	17 (77%)	72 (83%)
Serious AE	4 (18.2%)	8 (9.2%)

Overall AEs were slightly higher in the co-administration group than simvastatin monotherapy group. The most common AEs were recorded in the body systems for GI, Infection and Infestations, and Musculoskeletal disorders; however, there was no predominant AE in either treatment group. Serious AEs occurred more frequently in the simvastatin group and evaluation of each individual reported SAE did not reveal a pattern of concern for either treatment group.

AEs within the liver and biliary system occurred more often in the co-administration group (7/87; 8%) than the simvastatin monotherapy group (1/22; 5%). One case in the co-administration group was reported as an SAE. This was a 37-year old female treated with eze + simva 40 mg in the base study then was assigned to eze + simva 10 mg in the extension study. The SAE for this patient was an elevated ALT observed during the final visit base study (ALT = 201 U/mL) that persisted on Day 13 of the extension study (ALT = 104 U/mL). The patient was discontinued from the study and subsequent LFTs

were normal. There were no clinical symptoms or other liver test abnormalities associated with this report. This was the only case of consecutive ≥ 3x ULN ALT/AST observed in this database. There were no cases of hepatitis or jaundice.

No cases of rhabdmyolysis or myopathy were reported. Only one patient had CK levels elevated between 5x and 10x ULN that was associated with back pain. This patient was on simvastatin 80 mg in the base study and assigned to eze + simva 10 mg in the extension period. The highest CK recorded was 1056 U/mL, 283 days into the extension study. Study drug was discontinued and CK levels subsequently decreased.

Protocol 2173C

Patients completing the base study P2173/P2246 (see Zetia® review) were eligible to enroll into this 48 week extension study. The base study evaluated the efficacy of adding ezetimibe 10 mg to a stable dose of statin versus continuing statin monotherapy in patients who were at or above their NCEP target goals. Approximately 40% and 30% of the base study patients were treated with atorvastatin or simvastatin, respectively. The remainder of the patients were treated with one of the other marketed statins at the time the study was being conducted. At the final visit of the base study, patients not receiving simvastatin monotherapy were converted, in an open-label manner, to an equipotent dose of simvastatin described in the clinical study report. This simvastatin "conversion" period lasted for 6 weeks. Upon completion of this conversion period, patients continued on this simvastatin dose but were re-randomized (4:1) into the following:

current dose of simvastatin + ezetimibe 10 mg daily (n=355)
current dose of simvastatin + placebo (n=78)

After 12 weeks on this new treatment assignment, patients not achieving their NCEP ATP II LDL goals had their simvastatin dose doubled. Titration continued until the goal was achieved or the maximum dose was reached (80 mg). The mean number of days on study therapy was 279.4 and 294.2 days for the simvastatin monotherapy and eze + simva groups, respectively.

A similar incidence of AEs was reported for the simvastatin monotherapy (72%) and eze + simva co-administration group (75%). Similar to the other 2 long-term studies, AEs were more commonly reported in the GI, Infections/infestation, and musculoskeletal body systems without a predominant event observed in one treatment group that could be considered of clinical relevance. There was only one death reported in this study which occurred in a patient receiving eze + simva 80. Death was secondary to trauma sustained in a motor vehicle accident.

There were no cases of hepatitis or jaundice in this study. One patient experienced consecutive > 3x ULN elevations of ALT or AST in the co-administration group versus none in the simvastatin group.

No cases of rhabdomyolysis were reported. One patient was reported as having myopathy but CK levels were not elevated. CK elevations of 3 to 5x ULN were reported in 3% of the simvastatin monotherapy group compared to <1% of the co-administered group. One patient treated with combination therapy had CK levels between 5 and 10x ULN and none experienced elevations above 10x ULN.

Other Safety Considerations

Postmarketing reports for Zetia® identified angioedema and rash and pancreatitis as adverse events meriting inclusion into labeling. The Office of Drug Safety also reviewed reports of bleeding in patients taking coumadin concomitantly with ezetimibe. Drug interaction studies between these two drugs have not revealed any changes in warfarin drug levels.

Overall AE rates summarized by Body System in the clinical studies have not revealed a signal that ezetimibe increases the risk of bleeding. In two studies, AEs reported under Platelet, Bleeding, or Clotting Disorders occurred in only a few patient; however, a higher rate was observed in the simvastatin monotherapy group compared to EZ + simvastatin group.

Table 14. AEs Reported Under Category of "Platelet, Bleeding, or Clotting Disorders"

Protocol	Simvastatin Monotherapy	EZ + Simvastatin
P2173	3/78 (4%)	5/355 (1%)
P0700	1/34 (3%)	1/66 (2%)

This reviewer specifically looked at clinical and laboratory AEs of patients in the controlled long-term studies who were treated with coumadin. Eighteen patients were identified who were taking coumadin in these studies. Of these, only two had an AE that was described as anemia or decreased Hct. Both of these patients were treated with ezetimibe + simvastatin 10 mg and neither had increases in PT or INR reported as an AE.

Based on the pK study and the clinical trial database, there is no evidence that ezetimibe increases the risk of bleeding associated with coumadin use and no changes to label are recommended.

Gallbladder-related adverse experiences were reported in several of the clinical studies. Thirteen patients were reported in the uncontrolled studies P0476 and P2134. Eight of these cases occurred while the patients were taking ezetimibe monotherapy, 2 involved the co-administration of ezetimibe and simvastatin, 1 involved ezetimibe and lovastatin, and 2 occurred prior to the initiation of ezetimibe or a statin. While the study investigators considered most of these cases to be unrelated to study drug, many had documented gallstones by radioimaging studies and many required cholecystectomy.

The following table summarizes gallbladder-related AEs in the controlled clinical studies.

Table 15. Incidence of Gallbladder Related AEs in Controlled LTE Clinical Studies

	Simvastatin Monotherapy	Ezetimibe + Simvastatin	Comments
Protocol 005X (AN7603, 7974, 7954, 7551)	0/229	4/539 (0.7%)	2 classified as serious 3/4 underwent cholecystectomy procedures all female

			2 reported as possibly drug related
Protocol 2173C (AN5061)	0/78	1/355 (0.3%)	female serious discontinued from study, refused surgery

4-month Safety Update (submitted January 23, 2004)
This submission included the study report for Protocol 038, a multicenter, randomized, double-blind, placebo-controlled, factorial design study comparing the ezetimibe 10/simva 10, 20, 40, and 80 mg combination tablets to corresponding doses of simvastatin alone and ezetimibe alone in patients with primary hypercholesterolemia. The study duration was 12 weeks after a 4 week diet/placebo run-in period. 1,528 patients entered this study (placebo = 148; EZ mono = 149; all simva = 622; all EZ + simva = 609). Patients completing this study were also eligible for an extension study; however, the study report for the extension study is not yet available for review with this application.

The safety findings from this study were similar to those submitted initially to the NDA. The incidence of consecutive > 3x ULN elevations in ALT and/or AST was similar across the treatment groups (0.7% for placebo, EZ mono, simva mono, and EZ/simva). Three additional cases of gallbladder-related AEs were reported in this study. All 3 involved women who were treated with ezetimibe and simvastatin. All underwent cholecystectomy.

Conclusions on Safety of Vytorin®
In the review of Zetia®, increases in hepatic transaminases were observed in the statin co-administration group compared to statin monotherapy and ezetimibe monotherapy. This finding is also evident in this application. For the long-term, controlled, clinical studies, the incidence of consecutive > 3x ULN elevations in ALT or AST was 1.7% for the ezetimibe + simvastatin group compared to 0.3% in the simvastatin monotherapy group. In the one study that had larger numbers of patients treated at the high dose of simvastatin in combination with ezetimibe (P005x), a dose relationship was observed for these transaminase elevations with the incidence being 5.8% for the 10/80 mg dose group. While no cases of hepatitis or serious liver injury resulted from these laboratory AEs, the label should accurately reflect the difference between Vytorin and simvastatin monotherapy and the increase rate of transaminase elevation with the highest fixed-dose combination tablet.

Twenty-one patients experienced a gallbladder-related adverse event including cholelithiasis, cholecystitis, acalculous cholecystitis, and gallbladder thickening. Two cases appear to have occurred while the subjects were still on placebo, eight occurred with ezetimibe monotherapy, and 11 involved ezetimibe co-administration with simvastatin (10) or lovastatin (1). The majority of subjects underwent surgery with full recovery. Most of these patients were female with an elevated BMI; both factors contributing to the development of gallstones. However, preclinical studies with

ezetimibe have documented an increase in gallbladder cholesterol levels that may suggest that these AEs are drug-related. This reviewer recommends that the label for Vytorin (and Zetia) discuss gallbladder-related adverse events under the ADVERSE REACTIONS section of the label.

PROPOSED LABELING

All FDA review disciplines have made comments on the proposed labeling. The reader is referred to the separate FDA reviews for detailed discussions of discipline-specific labeling changes.

The sponsor is proposing the following indications for Vytorin®:

Primary Hypercholesterolemia

VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

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

Based on the review of Protocols 005, 068, 038, and 1030, the medical reviewer recommends approval of Vytorin® for these indications.

Recommendations to the CLINICAL PHARMACOLOGY, WARNINGS, and ADVERSE REACTIONS sections of the label have been made by this reviewer based on her review of clinical efficacy and safety data for Vytorin® or the coadministration of ezetimibe and simvastatin. Please see Clinical Efficacy and Safety review sections and final approved labeling for details of these recommendations.

FINANCIAL DISCLOSURE

NDA 21-687 is a joint venture between Merck & Co., Inc. and Schering Plough. Both companies submitted financial disclosure information.

Financial information pertained to the following studies:

- A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 When Added to Ongoing Therapy with an HMG-CoA Reductase Inhibitor (Statin) in Patients with Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factor (Protocol 001);
- A Multicenter, Double-Blind, Randomized; Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 When Added to Ongoing Therapy with an HMG-CoA Reductase Inhibitor (Statin) in patients with Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factor (Protocol 002);
- A Multicenter, Double-Blind, Randomized Placebo-Controlled, "Factorial" Design, 12-Week Study to Evaluate the Efficacy of SCH 58235 10 mg/day Coadministered with Multiple Doses of Simvastatin in Patients with Primary Hypercholesterolemia. Extension Study- 48 Weeks. (Protocol P005 and P005X1);

- A Phase III, Double-Blind Efficacy and Safety Study of One Dose of SCH 52385 (10 mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 006);
- A Phase III Double-Blind Efficacy and Safety Study of One Dose of SCH 52385 (10 mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 007);
- Long-Term, Open-Label, Safety and Tolerability Study of SCH 52385 in Subjects with Primary Hypercholesterolemia (Protocol P008);
- A Phase III Double-Blind Efficacy and Safety Study of SCH 52385 (10 mg) in Addition to Simvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 011);
- Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia who have Previously Completed the 12-Week Double-Blind Study (Protocol P 014);
- Long-Term Safety and Tolerability Study of SCH 58235 or Placebo in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia (P 015);
- A Randomized, Double-Blind, Parallel, Multicenter Study to Evaluate the Efficacy and Safety of Simvastatin Monotherapy Compared with Simvastatin and Ezetimibe (SCH 58235) in Type 2 Diabetics Treated with Thiazolidenidiones (Protocol P 021);
- Comparison of Treatment with Ezetimibe (SCH 58235) and Simvastatin Coadministration Versus Simvastatin in Attaining NCEP ATP III Coronary Heart Disease or Cardiovascular Heart Disease Risk Equivalent Strata (Protocol P 023);
- A Multicenter, Double-Blind, Randomized, Parallel Group, 28-Week Study to Evaluate Efficacy and Safety of Ezetimibe and Simvastatin Coadministration Versus Atorvastatin in Patients with Primary Hypercholesterolemia (Protocol P 025);
- Open-Label, Randomized, 2-Part, 2-Period Crossover Study to Evaluate the Definitive Bioequivalence after Concomitant Administration of Single Doses of Ezetimibe and Simvastatin as Individual Tablets and as Final Market Image Ezetimibe/Simvastatin 10/10 mg (Protocol P 039);
- A Phase III Double-Blind Efficacy and Safety Study of One Dose of SCH 58235 (10mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol P 474);
- A Phase III Double-Blind, Efficacy and Safety Study of SCH 52385 (10 mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol P 475);
- Long-Term, Open-Label Safety and Tolerability Study of SCH 58235 in Subjects with Primary Hypercholesterolemia (Protocol P 476);
- Phase III, Double-Blind, Efficacy and Safety Study of SCH 58235 (10 mg) in addition to Simvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (P 0680);
- Phase III, Double-Blind , Efficacy and Safety Study of SCH 58235 (10 mg) in Addition to Simvastatin in Subjects with Coronary Heart Disease or Multiple Risk Factor and with Primary Hypercholesterolemia Not Controlled by Starting Dose (20 mg) of Simvastatin (Protocol P 0700);
- Long-Term, Open-Label Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia Who Have Previously Completed the 12-Week Double-Blind Study Protocol P00679 or P00680 (Protocol P 02134);
- Long-Term Safety and Tolerability Study of SCH 58235 or Placebo in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia (Protocol P 02156);

PEDIATRIC REQUIREMENTS

At the End-of-Phase 2 meeting, the applicant requested and was granted a pediatric waiver for children < 10 years of age and a deferral for children 10 years to < 18 years of age.

CONCLUSIONS

Vytorin® is a fixed-dose combination drug product containing ezetimibe 10 mg with simvastatin 10, 20, 40, or 80 mg. In a definitive BE study, the applicant has demonstrated that the lowest and highest doses of Vytorin are bioequivalent to the individual components coadministered. Based on dissolution studies and dose-proportionality studies, a biowaiver was granted for the intermediate doses of Vytorin 10/20 and 10/40. The findings from the clinical pharmacology studies support the bridging of data from the Zetia® application to this NDA. The sponsor has elected to conduct additional clinical studies of the coadministration of ezetimibe and simvastatin and the to-be-marketed product. Based on the results of all trials reviewed under NDA 21-687, this reviewer has concluded that Vytorin® is a safe and effective drug for the labeled indications.

RECOMMENDATIONS

Pending labeling negotiations, this application should be approved.

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

/s/

Mary Parks
7/13/04 08:52:14 AM
MEDICAL OFFICER

David Orloff
7/15/04 05:10:02 PM
MEDICAL OFFICER