WPC-MK0653-T-102015

PRODUCT CIRCULAR

Tablets
EZETROL®
(ezetimibe)

I. THERAPEUTIC CLASS

EZETROL (ezetimibe) is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols.

II. INDICATIONS

Primary Hypercholesterolemia

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

EZETROL, administered in combination with fenofibrate, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

EZETROL, administered with 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 (Phytosterolemia)

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

III. CLINICAL PHARMACOLOGY

IIIa. Mechanism of Action:

EZETROL is orally active and potent, with a unique mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion (like bile acid sequestrants) and does not inhibit cholesterol synthesis in the liver (like statins).

In a 2-week clinical study in 18 hypercholesterolemic patients, EZETROL inhibited intestinal cholesterol absorption by 54%, compared with placebo. By inhibiting the absorption of intestinal cholesterol, ezetimibe reduces the delivery of cholesterol to the liver. Statins reduce cholesterol synthesis in the liver. Together these distinct mechanisms provide complementary cholesterol reduction. EZETROL, administered with a statin, is effective in improving serum total-C, LDL-C, Apo B, TG and HDL-C in patients with hypercholesterolemia, beyond either treatment alone. Administration of EZETROL with fenofibrate is effective in improving serum total-C, LDL-C, Apo B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

Clinical studies demonstrate that elevated levels of total-C, LDL-C and Apo B, the major protein constituent of LDL, promote human atherosclerosis. In addition, decreased levels of HDL-C are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very-low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and remnants, can also promote atherosclerosis.

A series of preclinical studies was performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

IIIb. Pharmacokinetics

IIIb-1. Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as EZETROL 10-mg tablets. EZETROL can be administered with or without food.

IIIb-2. Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

IIIb-3. Metabolism

Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20% and 80 to 90% of the total drug in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

IIIb-4. Elimination

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

IIIb-5. Characteristics in Patients (Special Populations)

Pediatric Patients

The pharmacokinetics of ezetimibe are similar between children ≥6 years and adults. Pharmacokinetic data in the pediatric population <6 years of age are not available. Treatment with EZETROL is not recommended for children less than 10 years old.

Geriatric Patients

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with EZETROL. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Insufficiency

After a single 10-mg dose of ezetimibe, the mean area under the curve (AUC) for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients (see VI. PRECAUTIONS).

Renal Insufficiency

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including cyclosporine) had a 12-fold greater exposure to total ezetimibe.

Gender

Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of gender.

Race

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians. There were too few patients in other racial or ethnic groups to permit

further pharmacokinetic comparisons.

IIIc. Clinical Studies

Primary Hypercholesterolemia

Monotherapy

In two, multicenter, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolemia, EZETROL 10 mg significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C compared to placebo (see Table 1). Reduction in LDL-C was consistent across age, sex and baseline LDL-C. Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of EZETROL. In addition, EZETROL had no effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, had no effect on prothrombin time, and did not impair adrenocortical steroid hormone production.

Table 1

Mean Response to EZETROL in Patients with Primary Hypercholesterolemia (Mean % Change from Baseline)

	Treatment group	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C
Study 1	Placebo	205	+1	+1	-1	-1	-1
	EZETROL	622	-12	-18	-15	-7	+1
Study 2	Placebo	226	+1	+1	-1	+2	-2
	EZETROL	666	-12	-18	-16	-9	+1
Pooled Data (Studies 1 & 2)	Placebo	431	0	+1	-2	0	-2
	EZETROL	1288	-13	-18	-16	-8	+1

[a] Median % change from baseline

Co-Administration with a Statin

EZETROL Initiated Concurrently with a Statin

In four, multicenter, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolemia, EZETROL 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. In general, the incremental effect on LDL-C reduction was independent of the dose or specific statin used. In addition, LDL-C reduction for EZETROL co-administered with the lowest tested dose (10 mg) of any of the statins was similar to or greater than the LDL-C reduction of the highest tested dose of the corresponding statin administered alone (Table 2).

Table 2

Mean % Change from Baseline in Plasma Concentration of Calculated LDL-C for EZETROL Administered with Statins

	Atorvastatin	Simvastatin	Pravastatin	Lovastatin

	Study	Study	Study	Study
Placebo	+4	-1	-1	0
EZETROL	-20	-19	-20	-19
10 mg statin	-37	-27	-21	-20
EZETROL + 10 mg statin	-53	-46	-34	-34
20 mg statin	-42	-36	-23	-26
EZETROL + 20 mg statin	-54	-46	-40	-41
40 mg statin	-45	-38	-31	-30
EZETROL + 40 mg statin	-56	-56	-42	-46
80 mg statin	-54	-45	-	-
EZETROL + 80 mg statin	-61	-58	-	-
Pooled data: All statin doses	-44	-36	-25	-25
Pooled data: All EZETROL + statin doses	-56	-51	-39	-40

In a pooled analysis of all EZETROL + statin doses, EZETROL had a beneficial effect on total-C, Apo B, TG, and HDL-C (Table 3).

Table 3

Pooled Analysis of the Mean % Change from Baseline in Total-C, Apo B, TG, and HDL-C

	Total-C	Apo B	TG[a]	HDL-C
EZETROL + Atorvastatin	-41	-45	-33	+7
Atorvastatin alone	-32	-36	-24	+4
EZETROL + Simvastatin	-37	-41	-29	+9
Simvastatin alone	-26	-30	-20	+7
EZETROL + Pravastatin	-27	-30	-21	+8
Pravastatin alone	-17	-20	-14	+7
EZETROL + Lovastatin	-29	-33	-25	+9
Lovastatin alone	-18	-21	-12	+4

[a] median % change

EZETROL Added to On-going Statin Therapy

In a multicenter, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (100 to 160 mg/dl, depending on baseline characteristics) were randomized to receive either EZETROL 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), LDL-C goal at study endpoint was achieved by 72% and 19% of patients randomized to EZETROL and placebo, respectively.

EZETROL, added to on-going statin therapy, significantly lowered total-C, LDL-C, Apo B, and TG and increased HDL-C, compared with placebo (Table 4). LDL-C reductions were consistent across all statins.

Table 4

Mean Response to Addition of EZETROL to On-going Statin Therapy[a] in Patients with Hypercholesterolemia (Mean % Change from Baseline)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[b]	HDL-C
On-going Statin +Placebo	390	-2	-4 (-6 mg/dl[c])	-3	-3	+1
On-going Statin +EZETROL	379	-17	-25 (-36 mg/dl[c])	-19	-14	+3

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)

[b] Median % change from baseline

[c] Change in LDL-C from baseline LDL-C (138 mg/dl and 139 mg/dl for statin + EZETROL and statin + placebo, respectively)

EZETROL or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

In a multicenter, double-blind, 14-week study, 621 patients with hypercholesterolemia receiving atorvastatin 10 mg daily with an LDL-C >130 mg/dl were randomized to receive atorvastatin 20 mg or EZETROL 10 mg added to atorvastatin 10 mg therapy. The atorvastatin dose could be titrated up to 80 mg in the atorvastatin arm and up to 40 mg in the EZETROL plus atorvastatin co-administration arm, based on patients not attaining LDL-C goal (<100 mg/dl). The mean baseline LDL-C was 187 mg/dl and approximately 60% of the patients had heterozygous familial hypercholesterolemia (HeFH). At study end, there was a significant difference in attainment of LDL-C goal between patients in the EZETROL co-administration arm (22%) and patients on atorvastatin monotherapy (7%). At week 4, there was a significant difference in LDL-C reductions between co-administration patients (24%; EZETROL + atorvastatin 10 mg) and monotherapy patients (9%; atorvastatin 20 mg). In the sub-group of patients with HeFH, similar results for LDL-C goal attainment and LDL-C reductions were achieved.

In a similarly designed study in 100 patients with hypercholesterolemia receiving simvastatin 20 mg and not at LDL-C goal, the addition of EZETROL 10 mg to simvastatin titration compared to titration of simvastatin alone produced similar advantages to those observed in the atorvastatin study described above. For example, significant differences in LDL-C goal attainment (27% for EZETROL + simvastatin vs. 3% for simvastatin alone) and LDL-C reductions (24% for EZETROL + simvastatin vs. 11% for simvastatin alone) were achieved.

Co-administration with Fenofibrate

In a multicenter, double-blind, placebo-controlled, clinical study in patients with mixed hyperlipidemia, 625 patients were treated for up to 12 weeks and 576 for up to an additional 48 weeks. Patients were randomized to receive placebo, EZETROL alone, 160 mg fenofibrate alone, or EZETROL and 160 mg fenofibrate in the 12-week study. After completing the 12-week study, eligible patients were assigned to EZETROL coadministered with fenofibrate or fenofibrate monotherapy for an additional 48 weeks.

EZETROL co-administered with fenofibrate significantly lowered total-C, LDL-C, Apo B, and non-HDL-C compared to fenofibrate administered alone. The percent decrease in TG and percent increase in HDL-C for EZETROL co-administered with fenofibrate were comparable to those for fenofibrate administered alone (see Table 5).

Table 5

Response to EZETROL and Fenofibrate Initiated Concurrently in Patients with Mixed Hyperlipidemia (Mean[a] % Change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Placebo	63	0	0	-1	-9	+3	0
EZETROL	185	-12	-13	-11	-11	+4	-15
Fenofibrate 160 mg	188	-11	-6	-15	-43	+19	-16
EZETROL + Fenofibrate 160 mg	183	-22	-20	-26	-44	+19	-30

[a] For triglycerides, median % change from baseline

[b] Baseline - on no lipid-lowering drug

The changes in lipid endpoints after an additional 48 weeks of treatment with EZETROL co-administered with fenofibrate or with fenofibrate alone were consistent with the 12-week data displayed above.

Homozygous Familial Hypercholesterolemia (HoFH)

A study was conducted to assess the efficacy of EZETROL in the treatment of HoFH. This double-blind, randomized, 12-week study enrolled 50 patients with a clinical and/or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving atorvastatin or simvastatin (40 mg). Patients were randomized to one of three treatment groups, atorvastatin or simvastatin (80 mg), EZETROL 10 mg administered with atorvastatin or simvastatin (40 mg), or EZETROL 10 mg administered with

atorvastatin or simvastatin (80 mg). Results are shown in Table 6. EZETROL, administered with atorvastatin (40 or 80 mg) or simvastatin (40 or 80 mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80 mg.

Table 6
Mean Response to EZETROL in Patients with HoFH (Mean % Change from Baseline)

Treatment (Daily Dose)	N	LDL-C
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-7
EZETROL + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-21
Sub-group analysis: EZETROL + Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-27

Prevention of Cardiovascular Disease

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a multicenter, randomized, double-blind, active-control study of 18,144 patients enrolled within 10 days of hospitalization for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). Patients had an LDL-C ≤125 mg/dL (≤3.2 mmol/L) at the time of presentation with ACS if they had not been taking lipid-lowering therapy, or ≤100 mg/dL (≤2.6 mmol/L) if they had been receiving lipid-lowering therapy. All patients were randomized in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

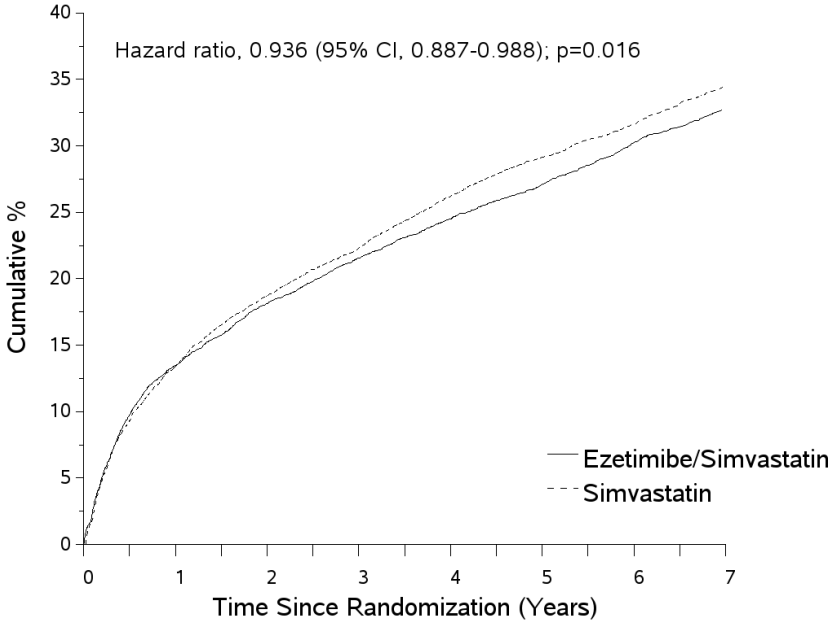
Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n=6390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n=11594). Prior to the hospitalization for the qualifying ACS event, 34% of the patients were on statin therapy. At one year, the average LDL-C for patients continuing on therapy was 53.2 mg/dL (1.4 mmol/L) for the ezetimibe/simvastatin group and 69.9 mg/dL (1.8 mmol/L) for the simvastatin monotherapy group. Lipid values were generally obtained for patients who remained on study therapy.

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalization, or any coronary revascularization procedure occurring at least 30 days after randomized treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe when added to simvastatin resulted in relative risk reduction of 6.4% in terms of the reduction in the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with

simvastatin alone (p=0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group (see Figure 1 and Table 7).

The treatment effect of ezetimibe/simvastatin was generally consistent with the overall results across many subgroups, including sex, age, race, medical history of diabetes mellitus, baseline lipid levels, prior statin therapy, prior stroke, and hypertension (see Figure 2).

Figure 1: Effect of Ezetimibe/Simvastatin on the Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke



Subjects at risk								
Ezetimibe/Simvastatin	9067	7371	6801	6375	5839	4284	3301	1906
Simvastatin	9077	7455	6799	6327	5729	4206	3284	1857

Figure 2: Subgroup Analysis of Primary Composite Endpoint of Cardiovascular Death, Major Coronary Event, or Non-fatal Stroke

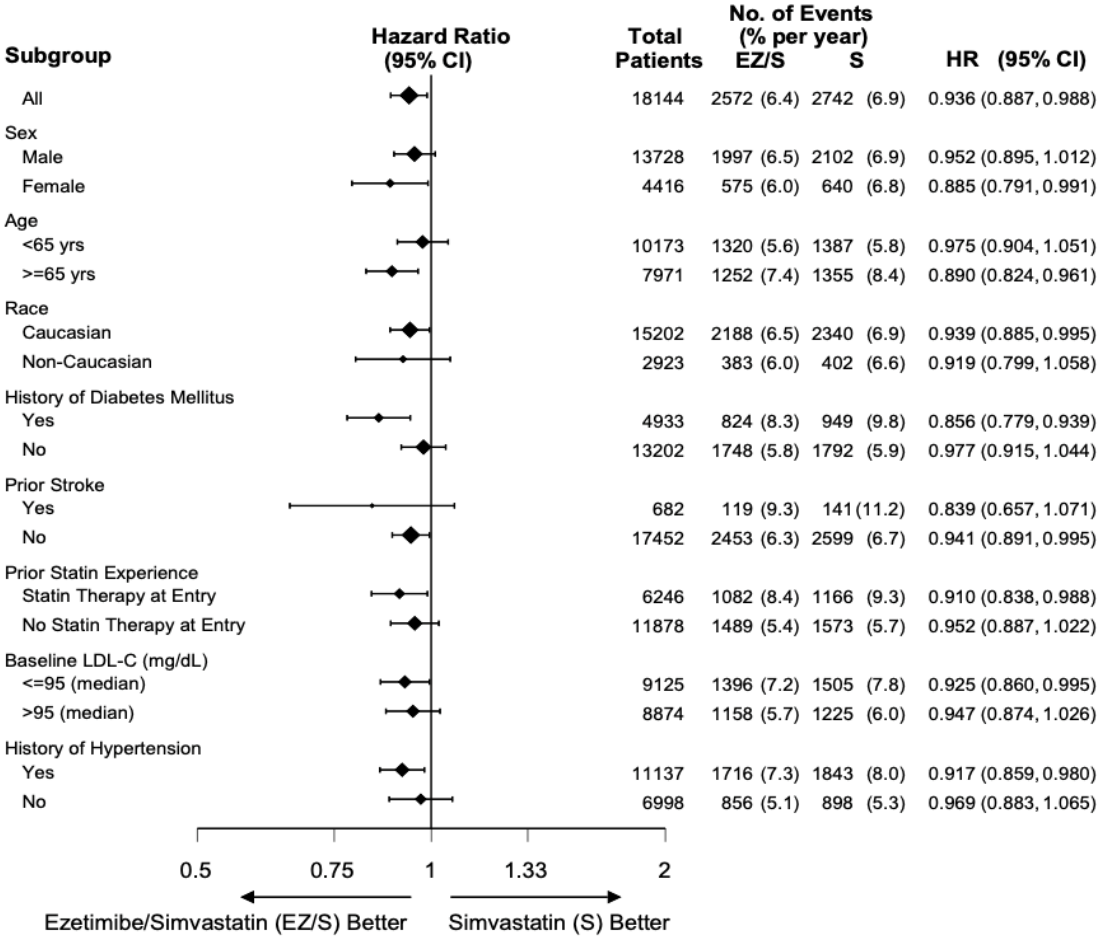


Table 7

Major Cardiovascular Events by Treatment Group in All Randomized Patients in IMPROVE-IT

Outcome	Ezetimibe/Simvastatin 10/40 mg* (N=9067)		Simvastatin 40 mg† (N=9077)		Hazard Ratio (95% CI)	p-value
	n	K-M %‡	n	K-M %‡		
Primary Composite Efficacy Endpoint (CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Secondary Composite Efficacy Endpoints						
CHD death, nonfatal MI, urgent coronary revascularization after 30 days	1322	17.52%	1448	18.88%	0.912 (0.847, 0.983)	0.016
MCE, non-fatal stroke, death (all causes)	3089	38.65%	3246	40.25%	0.948 (0.903, 0.996)	0.035
CV death, non-fatal MI, unstable angina requiring hospitalization, any revascularization, non-fatal stroke	2716	34.49%	2869	36.20%	0.945 (0.897, 0.996)	0.035

Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalization	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularization after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010
All MI (fatal and non-fatal)	977	13.13%	1118	14.82%	0.872 (0.800, 0.950)	0.002
All stroke (fatal and non-fatal)	296	4.16%	345	4.77%	0.857 (0.734, 1.001)	0.052
Non-hemorrhagic stroke§	242	3.48%	305	4.23%	0.793 (0.670, 0.939)	0.007
Hemorrhagic stroke	59	0.77%	43	0.59%	1.377 (0.930, 2.040)	0.110
Death from any cause	1215	15.36%	1231	15.28%	0.989 (0.914, 1.070)	0.782

* 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.

† 27% were uptitrated to simvastatin 80 mg.

‡ Kaplan-Meier estimate at 7 years.

§ includes ischemic stroke or stroke of undetermined type.

Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)

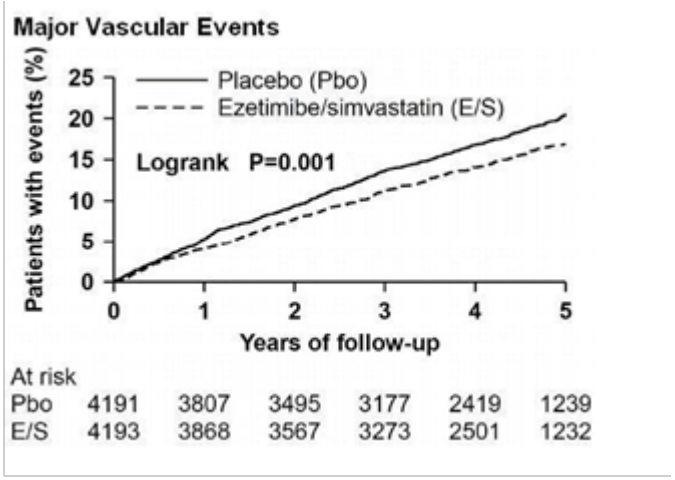
The Study of Heart and Renal Protection (SHARP) was a multinational, randomized, placebo-controlled, double-blind study conducted in 9438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. For the first year, patients were randomized in a ratio of 4:4:1, respectively, to a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg, placebo, or simvastatin 20 mg daily. The 1-year simvastatin arm was included to enable the comparison of EZETROL combined with simvastatin to simvastatin alone with regard to safety and lipids. At 1 year the simvastatin-only arm was re-randomized 1:1 to a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg or placebo. A total of 4650 patients were allocated to EZETROL 10 mg combined with simvastatin 20 mg and 4620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 and 63% were male, 72% Caucasian, 23% diabetic and, for those not on dialysis, the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 108 mg/dL. As of the 1-year measurement, LDL-C was reduced 26% relative to placebo by simvastatin 20 mg alone and 38% for EZETROL 10 mg combined with simvastatin 20 mg. At the midpoint of the

study (2.5 years) mean LDL-C reduction in all randomized patients for EZETROL combined with simvastatin relative to placebo was 32%. All lipid measurements included patients no longer taking study medication.

The SHARP protocol-specified primary comparison was an intention-to-treat analysis of "major vascular events" (MVE; defined as nonfatal MI or cardiac death, stroke, or any revascularization procedure) in only those patients initially randomized to the EZETROL combined with simvastatin (n=4193) or placebo (n=4191) groups. Secondary analyses included the same composite analyzed for the full cohort randomized (at study baseline or at year 1) to EZETROL combined with simvastatin (n=4650) or placebo (n=4620) as well as the components of this composite.

The primary endpoint analysis showed that EZETROL combined with simvastatin significantly reduced the risk of major vascular events (749 patients with events in the placebo group vs. 639 in the EZETROL combined with simvastatin group) with a relative risk reduction of 16% (p=0.001) (see Figure 3).

Figure 3: Effect of EZETROL Combined with Simvastatin on the Primary Endpoint of Risk of Major Vascular Events



The individual components of MVE in all randomized patients are presented in Table 8. EZETROL combined with simvastatin significantly reduced the risk of stroke and any revascularization, with non-significant numerical differences favoring EZETROL combined with simvastatin for nonfatal MI and cardiac death.

Table 8
Major Vascular Events by Treatment Group in All Randomized Patients in SHARP[a]

Outcome	EZETROL 10 mg combined with simvastatin 20 mg (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P-value
Major Vascular Events	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.001
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.004
Major Atherosclerotic Events (MAE)[b]	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.002

[a] Intention-to-treat analysis on all SHARP patients randomized to EZETROL combined with simvastatin or placebo either at baseline or year 1.

[b] MAE defined as the composite of nonfatal myocardial infarction, coronary death, non-hemorrhagic stroke, or any revascularization.

Nevertheless, this study design did not allow for a separate contribution of the ezetimibe or simvastatin to efficacy to significantly reduce the risk of major vascular events in patients with CKD.

The absolute reduction in LDL cholesterol achieved with EZETROL combined with simvastatin was lower among patients with a lower baseline LDL-C (<2.5 mmol/l) and patients on dialysis at baseline than the other patients, and the corresponding risk reductions in these two groups were attenuated.

Homozygous Sitosterolemia (Phytosterolemia)

A study was conducted to assess the efficacy of EZETROL in the treatment of homozygous sitosterolemia. In this multicenter, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolemia were randomized to receive EZETROL 10 mg (n=30) or placebo (n=7). EZETROL significantly lowered the two major plant sterols, sitosterol and campesterol, by 21% and 24% from baseline, respectively. In contrast, patients who received placebo had increases in sitosterol and campesterol of 4% and 3% from baseline, respectively. For patients treated with EZETROL, the reduction in plant sterols was progressive over the course of the study.

Reductions in sitosterol and campesterol were consistent between patients taking EZETROL concomitantly with bile acid sequestrants (n=8) and patients not on concomitant bile acid sequestrant therapy (n=21).

IV. DOSAGE AND ADMINISTRATION

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with EZETROL.

The recommended dose of EZETROL is 10 mg once daily, used alone, with a statin, or with fenofibrate. EZETROL can be administered at any time of the day, with or without food.

Patients with Renal Impairment

Monotherapy

In patients with renal impairment, no dosage adjustment of EZETROL is necessary (see IIIb-5. Characteristics in Patients [Special Populations]).

Combination Therapy with Simvastatin

In patients with mild renal impairment (estimated GFR ≥60 mL/min/1.73 m^2), no dosage adjustment of EZETROL or simvastatin is necessary. In patients with chronic kidney disease and estimated glomerular filtration rate <60 mL/min/1.73 m^2, the dose of EZETROL is 10 mg and the dose of simvastatin is 20 mg once a day in the evening. In such patients, the use of higher doses of simvastatin should be closely monitored (see VI. PRECAUTIONS, IIIb-5. Characteristics in Patients [Special Populations] and IIIc. CLINICAL STUDIES).

Use in the Elderly

No dosage adjustment is required for elderly patients (see IIIb-5. Characteristics in Patients [Special Populations]).

Use in Pediatric Patients

Children and adolescents ≥10 years: No dosage adjustment is required (see IIIb-5. Characteristics in Patients [Special Populations]).

Children <10 years: Treatment with EZETROL is not recommended.

Use in Hepatic Impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6).

Treatment with ezetimibe is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score >9) liver dysfunction (see VI. PRECAUTIONS and IIIb-5. Characteristics in Patients [Special Populations]).

Co-administration with bile acid sequestrants

Dosing of EZETROL should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

V. CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

The combination of EZETROL with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All statins and fenofibrate are contraindicated in pregnant and nursing women. When EZETROL is administered with a statin or with fenofibrate in a woman with childbearing potential, refer to the product labeling for that medication.

VI. PRECAUTIONS

When EZETROL is to be administered with a statin or with fenofibrate, please refer to the Package Insert for that particular medication.

Liver Enzymes

In controlled co-administration trials in patients receiving EZETROL with a statin, consecutive transaminase elevations (≥3 X the upper limit of normal [ULN]) have been observed. When EZETROL is co-administered with a statin, liver function tests should be performed at initiation of therapy and according to the recommendations of the statin (see X. SIDE EFFECTS).

In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or

simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see X. SIDE EFFECTS).

In a controlled clinical study in which over 9000 patients with chronic kidney disease were randomized to receive EZETROL 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up period of 4.9 years), the incidence of consecutive elevations of transaminases (>3 X ULN) was 0.7% for EZETROL combined with simvastatin and 0.6% for placebo (see X. SIDE EFFECTS).

Skeletal Muscle

In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with EZETROL compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CPK >10 X ULN was 0.2% for EZETROL vs 0.1% for placebo, and 0.1% for EZETROL co-administered with a statin vs 0.4% for statins alone.

In post-marketing experience with EZETROL, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating EZETROL. However, rhabdomyolysis has been reported very rarely with EZETROL monotherapy and very rarely with the addition of EZETROL to agents known to be associated with increased risk of rhabdomyolysis. All patients starting therapy with EZETROL should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. EZETROL and any statin that the patient is taking concomitantly should be immediately discontinued if myopathy is diagnosed or suspected. The presence of these symptoms and a creatine phosphokinase (CPK) level >10 times the ULN indicates myopathy.

In IMPROVE-IT, 18,144 patients with CHD were randomized to receive ezetimibe/simvastatin 10/40 mg daily (n=9067) or simvastatin 40 mg daily (n=9077). During a median follow-up of 6.0 years, the incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury (see X. SIDE EFFECTS).

In a clinical trial in which over 9000 patients with chronic kidney disease were randomized to receive EZETROL 10 mg combined with simvastatin 20 mg daily (n=4650) or placebo (n=4620) (median follow-up 4.9 years), the incidence of myopathy/rhabdomyolysis was 0.2% for EZETROL combined with simvastatin and 0.1% for placebo (see X. SIDE EFFECTS).

Hepatic Insufficiency

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, EZETROL is not recommended in these patients (see IIIb-5. Characteristics in Patients [Special Populations]).

Fibrates

The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL and fibrates (other than fenofibrate) is not recommended (see IX. DRUG INTERACTIONS).

Fenofibrate

If cholelithiasis is suspected in a patient receiving EZETROL and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see X. SIDE EFFECTS and the Package Insert for fenofibrate).

Cyclosporine

Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL and cyclosporine. The degree of increase in ezetimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by ezetimibe (see IX. DRUG INTERACTIONS).

Anticoagulants

If EZETROL is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalized Ratio (INR) should be appropriately monitored (see IX. DRUG INTERACTIONS).

VII. PREGNANCY

No clinical data on exposed pregnancies are available. Animal studies of ezetimibe administered alone do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal

development, parturition or postnatal development. However, note that all statins and fenofibrate are contraindicated in pregnant women. Ezetimibe should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

When ezetimibe was given with lovastatin, simvastatin, pravastatin or atorvastatin, no teratogenic effects were observed in embryo-fetal development studies in pregnant rats. In pregnant rabbits, a low incidence of skeletal malformations was observed.

When ezetimibe is to be administered with a statin, please refer to the Package Insert for that particular statin.

VIII. NURSING MOTHERS

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

IX. DRUG INTERACTIONS

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration. Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Antacids: Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental LDL-C reduction

due to adding ezetimibe to cholestyramine may be lessened by this interaction.

Cyclosporine: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone (see VI. PRECAUTIONS).

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see X. SIDE EFFECTS and IIIc. CLINICAL STUDIES, Co-administration with Fenofibrate); co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, coadministration of EZETROL with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

Statins: No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, or rosuvastatin.

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. There have been post-marketing reports of increased International Normalized Ratio in patients who had EZETROL added to warfarin or fluindione. Most of these patients were also on other medications (see VI.

PRECAUTIONS).

X. SIDE EFFECTS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Liver enzyme abnormalities [see VI. PRECAUTIONS, Liver Enzymes)]
- Rhabdomyolysis and myopathy [see VI. PRECAUTIONS, Skeletal Muscle]

Monotherapy Studies:

In the EZETROL controlled clinical trials database (placebo-controlled) of 2396 patients with a median treatment duration of 12 weeks (range 0 to 39 weeks), 3.3% of patients on EZETROL and 2.9% of patients on placebo discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with EZETROL that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Arthralgia (0.3%)
- Dizziness (0.2%)
- Gamma-glutamyltransferase increased (0.2%)

The most commonly reported adverse reactions (incidence ≥2% and greater than placebo) in the EZETROL monotherapy controlled clinical trial database of 2396 patients were: upper respiratory tract infection (4.3%), diarrhea (4.1%), arthralgia (3.0%), sinusitis (2.8%), and pain in extremity (2.7%).

Statin Co-Administration Studies:

In the EZETROL + statin controlled clinical trials database of 11,308 patients with a median treatment duration of 8 weeks (range 0 to 112 weeks), 4.0% of patients on EZETROL + statin and 3.3% of patients on statin alone discontinued due to adverse reactions. The most common adverse reactions in the group of patients treated with EZETROL + statin that led to treatment discontinuation and occurred at a rate greater than statin alone were:

- Alanine aminotransferase increased (0.6%)
- Myalgia (0.5%)
- Fatigue, aspartate aminotransferase increased, headache, and pain in extremity (each at 0.2%)

The most commonly reported adverse reactions (incidence ≥2% and greater than statin alone) in the EZETROL + statin controlled clinical trial database of 11,308 patients were: nasopharyngitis (3.7%), myalgia (3.2%), upper respiratory tract infection (2.9%), arthralgia (2.6%) and diarrhea (2.5%).

Clinical Trial Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Monotherapy:

In 10 double-blind, placebo-controlled clinical trials, 2396 patients with primary hyperlipidemia (age range 9-86 years, 50% women, 90% Caucasians, 5% Blacks, 3% Hispanics, 2% Asians) and elevated LDL-C were treated with EZETROL 10 mg/day for a median treatment duration of 12 weeks (range 0 to 39 weeks).

Adverse reactions reported in ≥2% of patients treated with EZETROL and at an incidence greater than placebo in placebo-controlled studies of EZETROL, regardless of causality assessment, are shown in Table 9.

Table 9

Clinical Adverse Events Occurring in ≥2% of Patients Treated with EZETROL and at an Incidence Greater than Placebo, Regardless of Causality

Body System/Organ Class Adverse Event	EZETROL 10 mg (%) n = 2396	Placebo (%) n = 1159
Gastro-intestinal system disorders		
Diarrhea	4.1	3.7
General disorders and administration site conditions		
Fatigue	2.4	1.5
Infections and infestations		
Influenza	2.0	1.5
Sinusitis	2.8	2.2
Upper respiratory tract infection	4.3	2.5
Musculo-skeletal system disorders		
Arthralgia	3.0	2.2
Pain in extremity	2.7	2.5

The frequency of less common adverse events was comparable between EZETROL and placebo.

Combination with a Statin:

In 28 double-blind, controlled (placebo or active-controlled) clinical trials, 11,308 patients with primary hyperlipidemia (age range 10-93 years, 48% women, 85% Caucasians, 7% Blacks, 4% Hispanics, 3% Asians) and elevated LDL-C were treated with EZETROL 10 mg/day concurrently with or added to on-

going statin therapy for a median treatment duration of 8 weeks (range 0 to 112 weeks).

The incidence of consecutive increased transaminases (≥3 X ULN) was higher in patients receiving EZETROL administered with statins (1.3%) than in patients treated with statins alone (0.4%) (see VI. PRECAUTIONS, Liver Enzymes).

Clinical adverse reactions reported in ≥2% of patients treated with EZETROL + statin and at an incidence greater than statin, regardless of causality assessment, are shown in Table 10.

Table 10

Clinical Adverse Reactions Occurring in ≥2% of Patients Treated with EZETROL Co-administered with a Statin and at an Incidence Greater than Statin, Regardless of Causality

Body System/Organ Class Adverse Event	All Statins* (%) n=9361	EZETROL + All Statins* (%) n=11,308
Gastro-intestinal system disorders		
Diarrhea	2.2	2.5
General disorders and administration site conditions		
Fatigue	1.6	2.0
Infection and infestations		
Influenza	2.1	2.2
Nasopharyngitis	3.3	3.7
Upper respiratory tract infection	2.8	2.9
Musculoskeletal system and connective tissue disorders		
Arthralgia	2.4	2.6
Back pain	2.3	2.4
Myalgia	2.7	3.2
Pain in extremity	1.9	2.1

*All Statins = all doses of all statins

Combination with Fenofibrate:

This clinical study involving 625 patients with mixed dyslipidemia (age range 20-76 years, 44% women, 79% Caucasians, 0.1% Blacks, 11% Hispanics, 5% Asians) treated for up to 12 weeks and 576 patients treated for up to an additional 48 weeks evaluated co-administration of EZETROL and fenofibrate. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (≥3 X ULN, consecutive) in hepatic transaminase levels were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy (n=188) and EZETROL co-administered with fenofibrate (n=183), respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (95% CI: 0.0%, 3.1%) and 1.7% (95% CI: 0.6%, 4.0%) for fenofibrate monotherapy and EZETROL co-administered with fenofibrate, respectively (see VI. PRECAUTIONS, Fenofibrate). The numbers of patients exposed to co-administration therapy as well as fenofibrate and

ezetimibe monotherapy were inadequate to assess gallbladder disease risk. There were no CPK elevations >10 X ULN in any of the treatment groups.

Patients with Coronary Heart Disease

In the IMPROVE-IT study (see IIIc. CLINICAL STUDIES), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n=9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n=9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN or two consecutive observations of CK ≥5 and <10 times ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 times ULN with evidence of renal injury, ≥5 X ULN and <10 X ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 X ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin (see VI. PRECAUTIONS). Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalizations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

Patients with Chronic Kidney Disease

In the Study of Heart and Renal Protection (SHARP) (see IIIc. CLINICAL STUDIES, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)), involving over 9000 patients treated with a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg daily (n=4650) or placebo (n=4620), the safety profiles were comparable during a median follow-up period of 4.9 years. In this trial, only serious adverse events and discontinuations due to any adverse events were recorded. Discontinuation rates due to adverse events were comparable (10.4% in patients treated with EZETROL combined with simvastatin, 9.8% in patients treated with placebo). The incidence of myopathy/rhabdomyolysis was 0.2% in patients treated with EZETROL combined with simvastatin and 0.1% in patients treated with placebo. Consecutive elevations of transaminases (>3X ULN) occurred in 0.7% of patients treated with EZETROL combined with simvastatin compared with 0.6% of patients treated with placebo (see VI. PRECAUTIONS). In this trial, there were no statistically significant increases in the incidence of pre-specified adverse events, including cancer (9.4% for EZETROL combined with simvastatin, 9.5% for placebo), hepatitis, cholecystectomy or complications of gallstones or pancreatitis.

Laboratory Values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was similar between EZETROL (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with EZETROL co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see VI. PRECAUTIONS).

Clinically important elevations of CPK (≥10 X ULN) in patients treated with EZETROL administered alone or co-administered with a statin were similar to elevations seen with placebo or statin administered alone, respectively.

Post-marketing Experience

Because the reactions below are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following additional adverse reactions have been identified during post-approval use of EZETROL: Hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; erythema multiforme; arthralgia; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis (see VI. PRECAUTIONS); elevations in liver transaminases; hepatitis; abdominal pain; thrombocytopenia; pancreatitis; nausea; dizziness; paresthesia; depression; headache; cholelithiasis; cholecystitis.

XI. OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, and 40 mg/day to patients with homozygous sitosterolemia for 26 weeks, was generally well tolerated.

A few cases of overdosage with EZETROL have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

XII. STORAGE

Do not store above 30°C (86°F). Store in the original package.

XIII. AVAILABILITY

EZETROL is available as 10 mg tablets in packs of 30’s.

Product Registrant:
Organon Singapore Pte. Ltd.
150 Beach Road
#36-01/08 Gateway West
Singapore 189720

Zuellig Pharma (B) Sdn Bhd
Unit 5, 1st floor,
Spg 607, Jalan Gadong,
Kg Beribi, BSB, BE1118
Brunei Darussalam

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ORGANON