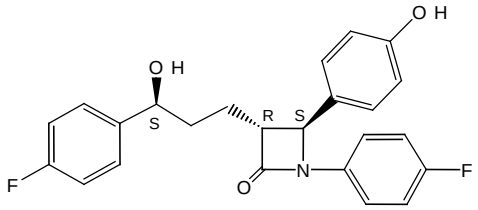
PRODUCT INFORMATION

EZETROL®
(ezetimibe)

NAME OF THE MEDICINE

EZETROL, ezetimibe is described chemically as 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone. The CAS registry number is 163222-33-1. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



DESCRIPTION

Ezetimibe is a white, crystalline powder that is freely to very soluble in ethanol, methanol, and acetone and practically insoluble in water. Ezetimibe has a melting point of about 163°C and is stable at ambient temperature.

Each tablet of EZETROL for oral administration contains 10 mg ezetimibe.

Each 10 mg tablet contains croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone and sodium lauryl sulfate.

PHARMACOLOGY

Mechanism of Action:

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

Ezetimibe has a mechanism of action that differs from other classes of cholesterol reducing compounds (eg statins, bile acid sequestrants [resins], fibric acid derivatives, and plant sterols.)

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 therefore 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 hypercholesterolaemic patients, EZETROL inhibited intestinal cholesterol absorption by 54 %, compared with placebo. By inhibiting the absorption of intestinal cholesterol, EZETROL 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, reduces total-C, LDL-C, Apo B, and TG and increases HDL-C in patients with hypercholesterolaemia, beyond either treatment alone.

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.

Pharmacokinetics

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.

Effect of Food on Oral Absorption

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.

Distribution

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

Metabolism

Ezetimibe is metabolised 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.

Excretion

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 faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma.

Characteristics in Patients (Special Populations)

Paediatric Patients

The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population <10years of age are not available. Clinical experience in paediatric and adolescent patients (ages 9 to 17) has been limited to patients with HoFH or sitosterolaemia.

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 is 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 PRECAUTIONS).

Renal Insufficiency

After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl $\leq$ 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 cyclosporin) 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 is 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.

CLINICAL TRIALS

Controlled clinical studies of varying designs were conducted with EZETROL either as monotherapy or co-administration with a statin. EZETROL significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB) and triglycerides (TG) and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

Primary Hypercholesterolemia

Monotherapy

In two, multicentre, double-blind, placebo-controlled, 12-week studies in 1719 patients with primary hypercholesterolaemia, 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, race, and baseline LDL-C. 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: Response to EZETROL in Patients with Primary Hypercholesterolaemia (Absolute and Percent Change from Baseline)

	Treatment group	N	Total-C Abs[a] (Pct[b])	LDL-C Abs[a] (Pct[b])	Apo B Abs[c] (Pct[b])	TG Abs[d] (Pct[e])	HDL-C Abs[a] (Pct[b])
Study 1	Placebo	205	+0.03 (+1%)	0.05 (+1%)	-0.03 (-1%)	-0.02 (-1%)	-0.02 (-1%)
	EZETROL	622	-0.81 (-12%)	-0.79 (-18%)	-0.26 (-15%)	-0.12 (-7%)	0.01 (+1%)
Study 2	Placebo	226	0.06 (+1%)	0.05 (+1%)	-0.03 (-1%)	0.03 (+2%)	-0.03 (-2%)
	EZETROL	666	-0.82 (-12%)	-0.77 (-18%)	-0.26 (-16%)	-0.15 (-9%)	0.01 (+1%)
Pooled Data (Studies 1 & 2)	Placebo	431	0.02 (0%)	0.04 (+1%)	-0.03 (-2%)	0.00 (0%)	-0.03 (-2%)
	EZETROL	1288	-0.84 (-13%)	-0.79 (-18%)	-0.26 (-16%)	-0.14 (-8%)	0.01 (+1%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline
[c] Mean absolute change from baseline, expressed as g/L
[d] Median absolute change from baseline, expressed as mmol/L
[e] Median percent change from baseline

Co-Administration with a Statin

EZETROL Initiated Concurrently with a Statin

In four, multicentre, double-blind, placebo-controlled, 12-week trials, in 1187 patients with hypercholesterolaemia, EZETROL 10 mg was administered alone or with various doses of atorvastatin, simvastatin, pravastatin, or lovastatin. The greatest LDL-C reducing effect is seen with the lowest dose of each statin, with only a further 2-9% incremental reduction in LDL-C with each doubling of the dose. Comparatively, adding 10mg of EZETROL to a given dose of a statin is shown to achieve a greater reduction in LDL-C than that achieved with statin dose doubling.

Table 2: Mean Absolute and Percent Change from Baseline in Plasma Concentration of Calculated LDL-C for EZETROL Administered with Statins

	Atorvastatin Study Abs[a] (Pct[b])	Simvastatin Study Abs[a] (Pct[b])	Pravastatin Study Abs[a] (Pct[b])	Lovastatin Study Abs[a] (Pct[b])
Placebo	0.20 (+4%)	-0.08 (-1%)	-0.03 (-1%)	0.00 (0%)
EZETROL	-0.92 (-20%)	-0.92 (-19%)	-0.91 (-20%)	-0.86 (-19%)
10 mg statin	-1.76 (-37%)	-1.25 (-27%)	-0.96 (-21%)	-0.94 (-20%)
EZETROL + 10 mg statin	-2.46 (-53%)	-2.10 (-46%)	-1.55 (-34%)	-1.56 (-34%)
20 mg statin	-1.91 (-42%)	-1.74 (-36%)	-1.10 (-23%)	-1.18 (-26%)
EZETROL + 20 mg statin	-2.59 (-54%)	-2.16 (-46%)	-1.82 (-40%)	-1.87 (-41%)
40 mg statin	-2.09 (-45%)	-1.75 (-38%)	-1.43 (-31%)	-1.44 (-30%)
EZETROL + 40 mg statin	-2.69 (-56%)	-2.55 (-56%)	-1.97 (-42%)	-2.15 (-46%)
80 mg statin	-2.57 (-54%)	-2.11 (-45%)	-	-
EZETROL + 80 mg statin	-2.93 (-61%)	-2.64 (-58%)	-	-
Pooled data: All statin doses	-2.08 (-44%)	-1.71 (-36%)	-1.16 (-25%)	-1.19 (-25%)
Pooled data: All EZETROL + statin doses	-2.67 (-56%)	-2.36 (-51%)	-1.78 (-39%)	-1.86 (-40%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline

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 Absolute and Percent Change from Baseline in Total-C, ApoB, TG, and HDL-C

	Total-C Abs[a] (Pct[b])	Apo B Abs[c] (Pct[b])	TG Abs[d] (Pct[e])	HDL-C Abs[a] (Pct[b])
EZETROL + Atorvastatin	-2.86 (-41%)	-0.78 (-45%)	-0.55 (-33%)	0.09 (+7%)
Atorvastatin alone	-2.24 (-32%)	-0.61 (-36%)	-0.40 (-24%)	0.05 (+4%)
EZETROL + Simvastatin	-2.49 (-37%)	-0.69 (-41%)	-0.53 (-29%)	0.11 (+9%)
Simvastatin alone	-1.78 (-26%)	-0.51 (-30%)	-0.32 (-20%)	0.09 (+7%)
EZETROL + Pravastatin	-1.86 (-27%)	-0.51 (-30%)	-0.36 (-21%)	0.10 (+8%)
Pravastatin alone	-1.17 (-17%)	-0.35 (-20%)	-0.26 (-14%)	0.08 (+7%)
EZETROL + Lovastatin	-1.96 (-29%)	-0.57 (-33%)	-0.44 (-25%)	0.10 (+9%)
Lovastatin alone	-1.25 (-18%)	-0.36 (-21%)	-0.21 (-12%)	0.04 (+4%)

[a] Mean absolute change from baseline, expressed as mmol/L
[b] Mean percent change from baseline
[c] Mean absolute change from baseline, expressed as g/L
[d] Median absolute change from baseline, expressed as mmol/L
[e] Median percent change from baseline

EZETROL Added to On-going Statin Therapy

In a multicentre, double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.59 to 4.14 mmol/L, depending on baseline characteristics) were randomised 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 randomised 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: Response to Addition of EZETROL to On-going Statin Therapy[a] in Patients with Hypercholesterolaemia (Absolute and Percent Change from Baseline)

	N	Total-C Abs[b] (Pct[c])	LDL-C Abs[b] (Pct[c])	Apo B Abs[d] (Pct[c])	TG Abs[e] (Pct[f])	HDL-C Abs[b] (Pct[c])
On-going Statin +Placebo	390	-0.16 (-2%)	-0.16 (-4%)	-0.05 (-3%)	-0.05 (-3%)	0.00 (+1%)
On-going Statin +EZETROL	379	-0.99 (-17%)	-0.92 (-25%)	-0.27 (-19%)	-0.19 (-14%)	0.03 (+3%)

[a] Percentages of patients receiving each statin: 40% atorvastatin, 31% simvastatin, 29% others (pravastatin, fluvastatin, cerivastatin, lovastatin)
[b] Mean absolute change from baseline, expressed as mmol/L
[c] Mean percent change from baseline
[d] Mean absolute change from baseline, expressed as g/L
[e] Median absolute change from baseline, expressed as mmol/L
[f] Median percent change from baseline

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

In a multicentre, double-blind, 14 week study, 621 patients with hypercholesterolaemia receiving atorvastatin 10 mg daily with an LDL-C > 3.36 mmol/L were randomised 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 (< 2.59 mmol/L). The mean baseline LDL-C was 4.84 mmol/L and approximately 60% of the patients had heterozygous familial hypercholesterolaemia (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 hypercholesterolaemia 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.

Other Studies

The use of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia demonstrated a numerically higher incidence of cholecystectomies in patients in the co-administration group compared with those in the monotherapy groups (see CONTRAINDICATIONS and ADVERSE EFFECTS). Each drug contributed to lowering LDL-C, but the effects on triglycerides and HDL-C were related to fenofibrate and were not enhanced by co-administration. Longer term clinical outcomes such as mortality and morbidity were not investigated.

Homozygous Familial Hypercholesterolaemia (HoFH)

A study was conducted to assess the efficacy of EZETROL in the treatment of HoFH. This double-blind, randomised, 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 (40mg). Patients were randomised to one of three treatment groups, atorvastatin or simvastatin (80mg), EZETROL 10mg administered with atorvastatin or simvastatin (40mg), or EZETROL 10mg administered with atorvastatin or simvastatin (80mg). Results are shown in Table 5. EZETROL, administered with atorvastatin (40 or 80mg) or simvastatin (40 or 80mg), significantly reduced LDL-C compared with increasing the dose of simvastatin or atorvastatin monotherapy from 40 to 80mg.

Table 5: Mean Response to EZETROL in Patients with HoFH (Mean Absolute and Percent Change from Baseline)

Treatment (Daily Dose)	N	LDL-C Abs[a] (Pct[b])
Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-0.51 (-7%)
EZETROL + Atorvastatin (40, 80 mg) or Simvastatin (40, 80 mg)	33	-1.76 (-21%)
Sub-group analysis: EZETROL + Atorvastatin (80 mg) or Simvastatin (80 mg)	17	-2.00 (-27%)

[a] Mean absolute change from baseline, expressed as mmol/L

[b] Mean percent change from baseline

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

The Study of Heart and Renal Protection (SHARP) was a multinational, randomised, placebo-controlled, double-blind study conducted in 9,438 patients with chronic kidney disease, a third of whom were on dialysis at baseline. Patients with a definite history of myocardial infarction (MI) or coronary revascularisation procedure, existing or planned renal transplant, recent acute uraemic emergency, evidence of active inflammatory muscle disease or creatine kinase (CK) >3xULN were excluded. For the first year, patients were randomised 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-randomised 1:1 to a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg or placebo. A total of 4,650 patients were allocated to EZETROL 10 mg combined with simvastatin 20 mg and 4,620 to placebo, and followed for a median of 4.9 years. Patients had a mean age of 62 (ranging in age from 39 to 94.5 years old); 63% were male, 72% were Caucasian and 23% were diabetic; and, for those not on dialysis, the median serum creatinine was 0.22 mmol/L and the mean estimated glomerular filtration rate (eGFR) was 26.5 mL/min/1.73 m^2, with 94% of patients having an eGFR < 45 mL/min/1.73 m^2. There were no lipid entry criteria. Mean LDL-C at baseline was 2.8 mmol/L. 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 randomised 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 revascularisation procedure) in only those patients initially randomised to the EZETROL combined with simvastatin (n=4,193) or placebo (n=4,191) groups. Secondary analyses included the same composite analysed for the full cohort randomised (at study

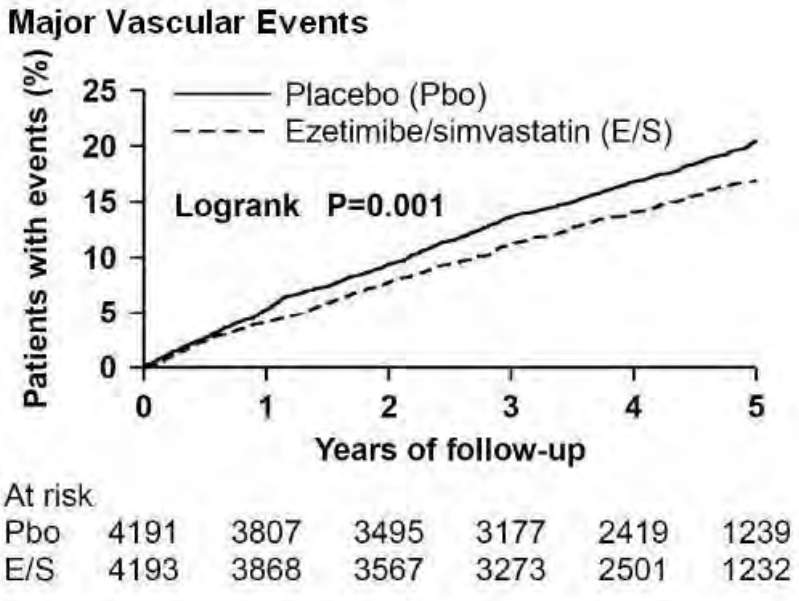
baseline or at year 1) to EZETROL combined with simvastatin (n=4,650) or placebo (n=4,620) as well as the components of this composite.

The primary endpoint analysis showed that EZETROL combined with simvastatin significantly reduced the risk of MVE (749 patients with events in the placebo group vs. 639 in the EZETROL combined with simvastatin group) with an absolute risk reduction of 2.3% (number needed to treat, 43) and a relative risk reduction of 16% (p=0.001) (see Figure 1). An analysis of major atherosclerotic events (MAE, a subset of the MVE composite that excluded non-coronary cardiac deaths and haemorrhagic stroke) showed that EZETROL combined with simvastatin significantly reduced the risk of MAE (526 (11.3%) of 4650 patients ever allocated to EZETROL combined with simvastatin and 619 (13.4%) of 4620 patients ever allocated to placebo), corresponding to an absolute risk reduction of 2.1% (number needed to treat, 48) and a relative risk reduction of 17% (p=0.002).

The risk reduction for the MVE composite was directionally consistent (i.e., EZETROL combined with simvastatin numerically superior to placebo) with that of the entire cohort of patients for the following key baseline predefined subgroups: age, gender, dialysis vs. non-dialysis, eGFR, diabetes, pre-existing atherosclerotic disease, blood pressure, or tertiles of baseline LDL-C.

Compliance rates with placebo and study medication declined over the course of the study. For example, at 20-25 months of follow-up, 68% of patients allocated to ezetimibe/simvastatin and 67% of patients allocated to placebo were taking 80% or more of the study medication, while at 44-49 months, compliance had fallen to 60% and 56%, respectively.

Figure 1: Effect of EZETROL Combined with Simvastatin on the Primary Endpoint of Risk of Major Vascular Events



The individual components of MVE in all randomised patients are presented in Table 6. EZETROL combined with simvastatin significantly reduced the risk of stroke and any revascularisation, with non-significant numerical differences favouring EZETROL combined with simvastatin for nonfatal MI and cardiac death.

Table 6: Major Vascular Events by Treatment Group in All Randomised Patients in SHARP[a]

Outcome	EZETROL 10 mg combined with simvastatin 20 mg (N=4,650)	Placebo (N=4,620)	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-haemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Haemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularisation	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 randomised 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-haemorrhagic stroke, or any revascularisation.

No significant treatment effect of EZETROL combined with simvastatin on MVE was found in the subgroup of patients on dialysis at baseline compared with those not on dialysis at baseline. Among 3023 patients on dialysis at baseline, EZETROL combined with simvastatin reduced the risk of MVE by 6% (RR 0.94: 95% CI 0.80-1.09) compared with 22% (RR 0.78: 95% CI 0.69-0.89) among 6247 patients not on dialysis at baseline (interaction P=0.08).

Among patients not on dialysis at baseline, EZETROL combined with simvastatin did not reduce the risk of progressing to end-stage renal disease compared with placebo.

There were no significant differences between the EZETROL combined with simvastatin and placebo groups on all cause mortality, or on any specific cause of death.

The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect, and was not able to provide evidence of efficacy for the combination of EZETROL 10 mg with simvastatin 20 mg compared to either the lower dose combination (i.e. EZETROL 10 mg with simvastatin 10 mg) or to treatment with statin alone (i.e. simvastatin 20 mg).

The effect of ezetimibe taken in combination with other statins in patients with CKD has not been studied.

Homozygous Sitosterolaemia (Phytosterolaemia)

A study was conducted to assess the efficacy of EZETROL in the treatment of homozygous sitosterolaemia. In this multicentre, double-blind, placebo-controlled, 8-week trial, 37 patients with homozygous sitosterolaemia were randomised 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).

INDICATIONS

Primary Hypercholesterolaemia

EZETROL administered alone, or with an HMG-CoA reductase inhibitor (statin), is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia.

Homozygous Familial Hypercholesterolaemia (HoFH)

EZETROL, administered with a statin, is indicated for patients with HoFH. Patients may also receive adjunctive treatments (e.g., LDL apheresis).

Homozygous Sitosterolaemia (Phytosterolaemia)

EZETROL is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolaemia.

CONTRAINDICATIONS

EZETROL is contraindicated in patients with hypersensitivity to any component of this medication.

When EZETROL is to be administered with a statin, please refer to the Product Information for that particular statin.

EZETROL in combination with fenofibrate is contraindicated in patients with gall bladder disease.

Therapy with EZETROL in combination with a statin is contraindicated during pregnancy and lactation.

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

PRECAUTIONS

When EZETROL is to be administered with a statin or fenofibrate, please refer to the Product Information for that particular product.

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 ADVERSEEFFECTS).

In a controlled clinical study in which over 9,000 patients with chronic kidney disease were randomised to receive EZETROL 10 mg with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620) (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 ADVERSEEFFECTS).

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 4 of 1674 (0.2%) patients administered EZETROL alone vs. 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered EZETROL and a statin vs. 4 of 929 (0.4%) patients administered a statin 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 a clinical trial in which over 9,000 patients with chronic kidney disease were randomised to receive EZETROL 10 mg combined with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620) (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 ADVERSE EFFECTS).

Hepatic Insufficiency

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

Paediatric (10 to 17 Years of Age) Patients

Ezetrol has not been studied in patients younger than 10 years of age or in pre-menarchal girls. (See DOSAGE AND ADMINISTRATION)

The long-term efficacy of therapy with Ezetrol in patients below 17 years of age to reduce morbidity and mortality in adulthood has not been studied.

Fibrates

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied and is therefore not recommended. (See INTERACTIONS WITH OTHER MEDICINES).

Fenofibrate

Fibrates may increase cholesterol excretion from the bile, and ezetimibe increased cholesterol in the gallbladder bile in a preclinical study in dogs. Given the potential for cholelithiasis, and the numerically higher incidence of cholecystectomies in patients administered ezetimibe and fenofibrate in a clinical study (see CLINICAL TRIALSand ADVERSE EFFECTS sections), coadministration of ezetimibe and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see CONTRAINDICATIONS).

Cyclosporin

Caution should be exercised when initiating ezetimibe in the setting of cyclosporin. Cyclosporin concentrations should be monitored in patients receiving EZETROL and cyclosporin (see INTERACTIONS WITH OTHER MEDICINES).

Anticoagulants

If EZETROL is added to warfarin, another coumarin anticoagulant or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (See INTERACTIONS WITH OTHER MEDICINES).

Genotoxicity

Ezetimibe alone or in combination with a statin (simvastatin, lovastatin, pravastatin or atorvastatin) or fenofibrate did not cause gene mutation in bacteria or chromosomal damage in human peripheral lymphocytes or bone marrow cells in mice.

Carcinogenicity

Two year dietary studies with ezetimibe alone in mice and rats showed no evidence of carcinogenic potential. The highest ezetimibe dose (500 mg/kg/day) in mice corresponds to exposure levels of approximately 4 and ≥150 times the adult human exposure for ezetimibe and total ezetimibe, respectively, based on AUC. Exposures in rats at the highest dose (1500 mg/kg/day in males and 500mg/kg/day in females) correspond to approximately 2 and 14 times the adult human exposure for ezetimibe and total ezetimibe respectively.

There are no carcinogenicity studies with ezetimibe/statin or ezetimibe/fenofibrate combinations.

Effects on Fertility

Ezetimibe had no effects on fertility in male and female rats at doses up to 1000mg/kg/day by oral gavage, corresponding to exposures of approximately 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively.

Use in Pregnancy [Pregnancy Category B3]

No clinical data on exposed pregnancies are available. Ezetimibe crossed the placenta in rats and rabbits. There was no evidence of foetal abnormalities in rats dosed with up to 1000 mg/kg/day of ezetimibe by oral gavage during organogenesis, corresponding to exposures of about 1 and 7 times the adult human exposure for ezetimibe and total ezetimibe respectively, based on AUC. There was an increase in the incidence of extra thoracic ribs in rabbits at doses of 250 to 1000 mg/kg/day, corresponding to exposures of 0.5 to 1 times and 100 to 150 times the adult human exposure for ezetimibe and total ezetimibe, respectively. The relevance of this finding to humans is not known. EZETROL should be used in pregnancy only if the potential benefit exceeds the potential risk. When EZETROL is to be administered with a statin, please refer to the Product Information for that particular statin.

Ezetimibe in combination with statins in rats and rabbits resulted in higher exposures to ezetimibe and/or statins than either drug administered alone. Skeletal malfunctions (hemivertebrae in rats and shortened /filamentous tail associated with fused and reduced number of caudal vertebrae in rabbits) and other less severe foetal abnormalities were observed in rats and rabbits dosed with ezetimibe/statin combinations during organogenesis. HMG-CoA reductase inhibitors (statins) are contraindicated during pregnancy, therefore, ezetimibe in combination with statins should not be used in pregnancy (see CONTRAINDICATIONS).

Embryofoetal studies in rats showed no adverse foetal effects of oral ezetimibe/fenofibrate doses corresponding to 5 times (total ezetimibe) and 38 times (fenofibric acid) the anticipated human plasma exposure at the maximum recommended doses. In similar studies in rabbits, a No Effect Level for embryotoxicity was established at *ca*. 90 times (total ezetimibe) and 32 times (fenofibric acid) anticipated human exposure levels.

Use in Lactation

Studies in rats have shown that ezetimibe is excreted in milk. Ezetimibe had no effects on pup development in rats treated with up to 1000 mg/kg/day of ezetimibe during late pregnancy and lactation. Drug exposures (based on AUC) in pups were approximately 1.5% and 50% of maternal exposures for ezetimibe and total ezetimibe respectively. It is not known whether ezetimibe is excreted into human breast milk. EZETROL should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use of machines have been performed. However, certain side effects that have been reported with EZETROL may affect some patients' ability to drive or operate machinery. Individual responses to EZETROL may vary (see ADVERSEEFFECTS).

INTERACTIONS WITH OTHER MEDICINES

In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolising enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolised 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.

Therefore, dosing of ezetimibe and a bile acid binding sequestrant should take place several hours apart. However, efficacy of such combination has not been studied.

Cyclosporin: The effect of cyclosporin on ezetimibe was studied in eight post-renal transplant patients with creatinine clearance of >50 mL/min who were on a stable dose of cyclosporin. 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 group of historical healthy volunteers (n=17) who had taken a single 10-mg dose of ezetimibe alone.

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 cyclosporin, 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 dose 100 mg dose of cyclosporin on Day 7 resulted in a mean 15% increase in cyclosporin AUC (range 10% decrease to 51% increase) compared to a single 100 mg dose of cyclosporin alone (see PRECAUTIONS).

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, or fluvastatin.

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

ADVERSE EFFECTS

Clinical studies of 8 to 14 weeks duration in which EZETROL 10 mg daily was administered alone, with a statin, or with fenofibrate in 3551 patients demonstrated: EZETROL was generally well tolerated, adverse reactions were usually mild and transient, the overall incidence of side effects reported with EZETROL was similar to that reported with placebo, and the discontinuation rate due to adverse experiences was comparable between EZETROL and placebo.

There were no drug-related adverse experiences reported occurring in ≥2% of patients taking EZETROL alone (n = 1691).

The following drug-related adverse experiences were reported occurring in ≥2% in patients taking EZETROL co-administered with a statin (n = 1675).

	All Statins (%) N=1676	EZETROL 10 mg Co-administered with a statin (%) N=1675
Musculoskeletal and connective tissue disorders		
Myalgia	2.4	3.2

In addition, the following common or uncommon drug-related adverse experiences were reported in clinical trials in patients taking EZETROL alone and at a greater incidence than placebo, or in patients taking EZETROL co-administered with a statin and at a greater incidence than statin administered alone.

EZETROL administered alone:
Investigations: Uncommon- gamma-glutamyltransferase increased; liver function test abnormal
Respiratory, Thoracic and Mediastinal Disorders: Uncommon- cough
Gastrointestinal Disorders: Common- abdominal pain; diarrhea; flatulence
Uncommon- dyspepsia; gastroesophageal reflux disease
Musculoskeletal and Connective Tissue Disorders: Uncommon- muscle spasms; neck pain
Metabolism and Nutrition Disorders: Uncommon- decreased appetite
Vascular Disorders: Uncommon- hot flush; hypertension
General Disorders and Administration Site Condition: Common-fatigue
Uncommon- chest pain; pain

EZETROL co-administered with a statin:
Investigations: Common- ALT and/or AST increased
Nervous System Disorders: Common- headache
Gastrointestinal Disorders: Uncommon- dry mouth; gastritis
Skin and Subcutaneous Tissue Disorders: Uncommon- pruritus
Musculoskeletal and Connective Tissue Disorders: Common- myalgia
Uncommon- back pain; muscular weakness; pain in extremity
General Disorders and Administration Site Condition: Uncommon- asthenia; edema peripheral

EZETROL co-administered with fenofibrate:
Gastrointestinal Disorders: Common- abdominal pain

In a co-administration study with fenofibrate (see CLINICAL TRIALS), in which 292 patients were exposed for ≥ 24 weeks and 120 exposed for ≥ 52 weeks, the incidence rate of cholecystectomy in the coadministration group was 1.7% (95% CI 0.6, 4.0) per 100 patient years compared to 0 (95% CI 0, 9.2) per 100 PY for the ezetimibe group and 0.6% (95% CI 0, 3.1) per 100 PY for the fenofibrate group. Longer term safety outcomes have not been studied.

Patients with Chronic Kidney Disease
In the Study of Heart and Renal Protection (SHARP) (see CLINICAL TRIALS, Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)), involving over 9,000 patients treated with a fixed dose combination of EZETROL 10 mg with simvastatin 20 mg daily (n=4,650) or placebo (n=4,620), 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. 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 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

The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment:
Hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria; erythema multiforme; arthralgia; myalgia; increased CPK; elevations of liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; dizziness; paraesthesia; depression; cholelithiasis; cholecystitis; constipation; asthenia and, very rarely myopathy/rhabdomyolysis (see PRECAUTIONS).

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 or with a statin. EZETROL can be administered at any time of the day, with or without food.

EZETROL may be administered with a statin for incremental effect. For convenience, the daily dose of EZETROL may be taken at the same time as the statin, according to the dosing recommendations for the statin.

Use in Renal Impairment/Chronic Kidney Disease

Monotherapy

In patients with renal impairment, no dosage adjustment of EZETROL is necessary (see 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 PRECAUTIONS, *Characteristics in Patients [Special Populations],* and CLINICAL TRIALS , Prevention of Major Vascular Events in Chronic Kidney Disease (CKD)).

Use in the Elderly

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

Paediatric Use

Initiation of treatment must be performed under review of a specialist.

Children and adolescents ≥ 10 years (pubertal status: boys Tanner Stage II and above and girls who are at least one year post-menarche): No dosage adjustment is required (see *Characteristics in Patients [Special Populations]*). The clinical experience in paediatric and adolescents patient (aged 10-17 years old) is however limited.

Children < 10 years: EZETROL is not recommended for use in children below age 10 due to insufficient data on safety and efficacy (see *Characteristics in Patients [Special Populations]*).

Hepatic InsufficiencyNo 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 CONTRAINDICATIONS, PRECAUTIONS and *Characteristics in Patients [Special Populations]*).

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, 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.

PRESENTATION AND STORAGE CONDITIONS

EZETROL – 10 mg, white to off-white capsule shaped tablets, debossed with “414” on one side. Supplied in blister packs of 5, 10 and 30.

Store below 30°C. Store in the original package.

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell Street
South Granville NSW 2142
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

23 June 2003

DATE OF MOST RECENT AMENDMENT

This document was approved by the Therapeutic Goods Administration on TBD.