Attachment 1: Product information for AusPAR Ezetimibe and Rosuvastatin Rosuzet Ezalo Merck Sharp & Dohme (Australia) Pty Limited PM-2013-02434-1-3 Date of Finalisation 29 January 2015. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

ROSUZET
[ezetimibe, rosuvastatin (as calcium)]

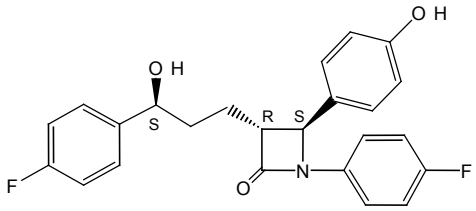
ROSUZET 10 mg/5 mg
ROSUZET 10 mg/10 mg
ROSUZET 10 mg/20 mg
ROSUZET 10 mg/40 mg

NAME OF THE MEDICINE

ROSUZET is a tablet containing ezetimibe 10mg and rosuvastatin (as calcium) 5, 10, 20 or 40 mg.

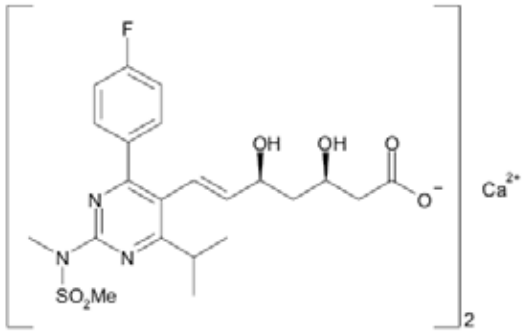
Ezetimibe

The chemical name is 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:



Rosuvastatin

The chemical name is bis [(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl] (3R, 5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The CAS Number is 147098-20-2. The empirical formula is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14 and its chemical structure 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.

Rosuvastatin calcium is an amorphous solid, which is slightly soluble in water (7.8 mg/mL at 37°C) and has a pKa of 4.6. Rosuvastatin calcium is the (3R,5S,6E) enantiomer.

ROSUZET is available for oral use as tablets containing 10 mg of ezetimibe and: 5.21 mg of rosuvastatin calcium, equivalent to 5 mg of rosuvastatin (ROSUZET 10/5);10.42 mg of rosuvastatin calcium, equivalent to 10 mg of rosuvastatin (ROSUZET 10/10); 20.84 mg of rosuvastatin calcium, equivalent to 20 mg of rosuvastatin (ROSUZET 10/20); or 40.67 mg of rosuvastatin calcium, equivalent to 40 mg of rosuvastatin (ROSUZET 10/40).

Each tablet of ROSUZET contains the following inactive ingredients: lactose, sodium lauryl sulfate, croscarmellose sodium, povidone, microcrystalline cellulose, sodium starch glycollate, magnesium stearate, pregelatinised maize starch, silicon dioxide.

PHARMACOLOGY

Mechanism of Action

Ezetimibe

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 (e.g. 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, ezetimibe 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. Ezetimibe, 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.

Rosuvastatin

Rosuvastatin is a fully synthetic competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver. Rosuvastatin produces its lipid-modifying effects in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I, is involved, amongst other functions, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C and TG, and low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to the lowering of non HDL-C (i.e. all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Pharmacokinetics

ROSUZET

ROSUZET has been shown to be bioequivalent to coadministration of corresponding doses of ezetimibe and rosuvastatin tablets.

In a pilot four period parallel design study of healthy hypercholesterolemic patients, primarily designed to evaluate the short term LDL lowering effects of ezetimibe 10 mg,

rosuvastatin 10 mg, ezetimibe 10 mg plus rosuvastatin 10 mg, and placebo, the pharmacokinetics of the compounds were also evaluated. The pharmacokinetic results from this study indicate that co-administration of ezetimibe 10 mg and rosuvastatin 10 mg would not result in the pharmacokinetics of either drug being significantly altered during co-administration compared to monotherapy.

This small, parallel groups study showed that there was no clinically meaningful effect on the AUC or C_{max} of ezetimibe, total ezetimibe (ezetimibe + conjugated ezetimibe) or rosuvastatin when ezetimibe 10 mg was co-administered with rosuvastatin 10 mg compared with ezetimibe 10 mg alone or rosuvastatin 10 mg alone. There was a small decrease in the mean AUC for ezetimibe and a small increase in the total ezetimibe mean AUC when comparing ezetimibe + rosuvastatin versus ezetimibe alone (97% [90% CI 70–133%] and 113% [90% CI 89–143%], respectively). There was a small increase in the mean C_{max} for ezetimibe and total ezetimibe when comparing ezetimibe + rosuvastatin versus ezetimibe alone (104% [90% CI 69–158%] and 118% [90% CI 83–170%], respectively). There was a small increase in the mean AUC and C_{max} for rosuvastatin during rosuvastatin and ezetimibe co-administration compared to rosuvastatin alone (119% [90% CI 87-162%] and 117% [90% CI 84-163%], respectively).

Although no pharmacokinetic studies of ezetimibe and rosuvastatin co-administration have been conducted in patients at increased risk of rosuvastatin exposure such as hepatic or renal impairment, there is the potential for increased exposure to rosuvastatin in patients receiving this combination.

Ezetimibe

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 10 mg tablets. Ezetimibe 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.

Rosuvastatin
In a bioequivalence study comparing 40 mg MSD ROSUVASTATIN tablets with the innovator's tablets, following an oral administration of a single-dose of MSD ROSUVASTATIN to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of rosuvastatin of approximately 26.18 ng/mL was achieved within approximately 3.62 hours (T_{max}).

Absorption
Peak plasma levels occur 5 hours after dosing. Absorption increases linearly over the dose range. Absolute bioavailability is 20%. The half-life is 19 hours and does not increase with increasing dose. There is minimal accumulation on repeated once daily dosing.

Distribution
Volume of distribution of rosuvastatin at steady state is approximately 134 litres. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin.

Metabolism
Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9, and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Excretion
Rosuvastatin undergoes limited metabolism (approximately 10%), mainly to the N-desmethyl form, and 90% is eliminated as unchanged drug in the faeces with the remainder being excreted in the urine.

Characteristics in Patients (Special Populations)

Paediatric Patients

ROSUZET
ROSUZET is not recommended for use in children.

Ezetimibe
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 < 10 years 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
Ezetimibe
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 ezetimibe. Therefore, no dosage adjustment is necessary in the elderly.

Hepatic Insufficiency
Ezetimibe
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
Ezetimibe
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
Ezetimibe

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

Ezetimibe

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

Rosuvastatin

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. However, pharmacokinetic studies, including one conducted in the US, have demonstrated an approximate 2-fold elevation in median exposure (AUC and C_{max}) in Asian subjects when compared with a Caucasian control group (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

All of the evidence for the efficacy of the combination of ezetimibe and rosuvastatin comes from short-term studies with surrogate endpoint. There have been no long-term studies with clinical outcome endpoints for this combination. The studies described include sponsor-initiated clinical trials and other placebo or comparator-controlled clinical trials from published literature.

Ezetimibe

Controlled clinical studies of varying designs were conducted with ezetimibe co-administered with a statin. Ezetimibe 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

Co-administration of Ezetimibe and Rosuvastatin

Ezetimibe Initiated Concurrently with Rosuvastatin

In a multicentre, randomised, open-label, parallel group study (EXPLORER[1]) in 469 subjects with hypercholesterolemia and a history of CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score > 20%) with fasting LDL-C levels between ≥ 4.1 mmol/L and < 6.5 mmol/L and fasting triglyceride (TG)

[1] Ballantyne CM, Weiss R., Moccetti T., Vogt A, Eber B, Sosef F, Duffield E. Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination With Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study). American Journal of Cardiology (2007) 99:5 (673-680).

concentration of < 4.52 mmol/L, subjects were randomly assigned either rosuvastatin 40 mg (n=230) or rosuvastatin 40 mg and ezetimibe 10 mg (n=239) for 6 weeks.

Treatment groups were similar at baseline in terms of demographic and clinical variables. In the rosuvastatin 40 mg group, the mean age of subjects was 63.5 years, 56% were male and 92% were Caucasian. 64% had metabolic syndrome and the mean baseline LDL-C was 4.95 mmol/L. In the rosuvastatin 40 mg + ezetimibe 10 mg group, the mean age of subjects was 63.1 years, 59% were male and 93% were Caucasian. 59% had metabolic syndrome and the mean baseline LDL-C was 4.90 mmol/L.

The primary end point was the percentage of patients achieving the ATP III LDL cholesterol goal (2.59 mmol/L) after 6 weeks of treatment. Significantly more patients who were treated with rosuvastatin 40 mg + ezetimibe 10 mg achieved the ATP III LDL cholesterol goal (< 2.6 mmol/L) at week 6 compared to those on rosuvastatin 40 mg alone (94.0% vs 79.1%, $p < 0.001$).

Secondary efficacy end points included percent change from baseline in LDL cholesterol, HDL cholesterol, TC, TG, non-HDL cholesterol, and other lipid parameters at Week 6. After 6 weeks, LDL cholesterol decreased to 1.47 and 2.11 mmol/L in the combination and monotherapy groups, respectively. Significantly greater percent decreases in LDL cholesterol levels were achieved with combination therapy than monotherapy (mean percent decrease -69.8% vs -57.1%, $p < 0.001$). Significantly ($p < 0.001$) greater decreases in TC, non-HDL cholesterol, and TGs were also observed at week 6 in the combination therapy group compared with the monotherapy group. Both treatments increased HDL cholesterol to a similar extent at week 6.

The percent of patients who discontinued treatment as a result of any adverse event was 2.5% for the combination therapy group and 1.3% for the monotherapy group.

Ezetimibe Added to Stable Rosuvastatin Therapy

In a multicentre, open-label, randomised, parallel-group 12-week study[2], 833 patients (458 male and 375 female, mean age 62 years) with hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD risk equivalent, atherosclerosis or a 10-year CHD Risk of >20% were randomised after a 6-week dietary lead-in period to rosuvastatin 10 mg, rosuvastatin 20 mg, simvastatin 40 mg or simvastatin 80 mg for 6 weeks. Ezetimibe 10 mg was then added to each regimen for a further 6 weeks.

The primary end point was percent change from baseline in LDL-C after 6 weeks combination therapy (Week 12). Ezetimibe added to rosuvastatin 10 mg and 20 mg lowered baseline LDL-C by 59.7% and 63.5% respectively, compared with 55.2% and 57.4% when added to simvastatin 40 mg and simvastatin 80 mg.

[2] Ballantyne CM, Schiebinger R, Cain V. Randomized comparison of rosuvastatin plus ezetimibe versus simvastatin plus ezetimibe: results of the GRAVITY study. Journal of the American College of Cardiology 55(10, Suppl. A): Abstract #1019-98, Mar 9, 2010.

Secondary end points included percent change in other lipid parameters after 6 weeks combination treatment. Ezetimibe 10mg+rosuvastatin 20 mg produced greater improvements in other lipid parameters than ezetimibe 10mg+simvastatin 40 mg/80 mg. Ezetimibe 10mg+rosuvastatin 10 mg significantly reduced LDL-C, TG, non-HDL-C, and Apo-B compared with Ezetimibe 10mg+Simvastatin 40 mg (**Table 1**).
Eighty-one patients did not complete the study; 31 withdrawals were due to adverse events.

Table 1: GRAVITY study – Percent change in lipid parameters and percent of patients achieving LDL-C goals at Week 12

	Study Group	R10mg+ E10mg (N=210)	R20mg+ E10mg (N=204)	S40mg+ E10mg (N=199)	S80mg+ E10mg (N=201)
	Baseline LDL-C (mg/dL; mean±SD)	162.7±22.7	164.8±24.7	164.8±23.6	163.1±24.1
Mean % change from baseline	LDL-C	-59.7*	-63.5† §	-55.2	-57.4
	HDL-C	6.4	7.5* ‡	3.9	4.3
	TG	-28.9*	-35.0† §	-23.0	-25.8
	Non-HDL-C	-54.7†	-58.9† §	-49.9	-52.4
	Apo-B	-46.1*	-49.5† §	-42.0	-44.2
% of patients achieving LDL-C goals	<100 mg/dL (<2.59 mmol/L)	93.3*	95.6† ‡	87.4	88.6
	<70 mg/dL (<1.81 mmol/L)	67.1	77.0† §	55.3	67.7
		*p<0.05 vs S40mg+ E10mg †p<0.001 vs S40mg+ E10mg	†p<0.001 vs S40mg+E10mg; ‡p<0.05 vs S80mg+E10mg; §p<0.001 vs S80mg+E10mg		

Ezetimibe Add-on to On-going Rosuvastatin Therapy (Titration Studies)

In a multicentre, randomised, double-blind, 6 week-active comparator study (P139V1), 440 subjects (272 male and 168 female) at moderately high/high risk of coronary heart disease with LDL cholesterol levels failing to reach their NCEP ATPIII goal (< 2.6 mmol/L or <1.8mmol/L depending on baseline characteristics) were stratified to treatment with rosuvastatin 5 mg or 10 mg for 4-5 weeks. Patients were then randomised to either doubling of their rosuvastatin dose (10 mg or 20 mg) or to add ezetimibe 10 mg to their rosuvastatin (5 or 10 mg) therapy.

Patients were 32 to 79 years of age with a mean baseline LDL-C of 2.69 mmol/L in the rosuvastatin (5 or 10 mg) + ezetimibe 10 mg group and 2.60 mmol/L in the rosuvastatin

(10 or 20 mg) group. The majority of patients were white (76.8%) and the majority (67.5%) were high risk for CHD with atherosclerotic vascular disease (AVD). Overall, the mean duration of hypercholesterolemia was 9.2 years.

The primary endpoint was percent change from baseline in LDL-C at Week 6 based on full analysis set population (all randomised patients excluding those who failed to receive at least one dose of study treatment or had lack of baseline data). The addition of ezetimibe 10 mg to rosuvastatin (5 mg or 10 mg) achieved significantly greater LDL-C reductions compared to doubling the initial dose of rosuvastatin (10 mg or 20 mg) ($p < 0.001$). The LS mean percent change in LDL-C from baseline to the study end was -20.96% when ezetimibe 10 mg was added to rosuvastatin and –5.71% when the original rosuvastatin dose was doubled (data pooled across the rosuvastatin 5 mg and 10 mg strata). The LS mean treatment difference was -15.25% with a 95% CI (-19.89, -10.60) (**Table 2**).

Table 2: Study P139V1 - Analysis of Percent Change from Baseline in LDL-Cholesterol (mg/dL) at Study Endpoint After 6 Weeks of Treatment

Treatment	N	Baseline (mg/dl) Mean ± SD	Endpoint (mg/dl) Mean ± SD	LS mean (95% CI)	Difference in LS Mean (95% CI)	P value
Overall						
ezetimibe 10mg + rosuvastatin (5 or 10mg)	219	103.90 ± 25.39	80.73 ± 32.28	-20.96 (-24.28, -17.64)	-15.25 (-19.89, -10.60)	< 0.001
Rosuvastatin (10 or 20mg)	217	100.20 ± 24.44	92.88 ± 26.52	-5.71 (-9.05, -2.38)		
Stratum I						
ezetimibe 10mg + rosuvastatin 5 mg	98	106.74 ± 23.54	85.89 ± 31.37	-17.92 (-22.69, -13.15)	-12.31 (-18.95, -5.67)	<0.001
Rosuvastatin 10 mg	96	102.42 ± 23.41	95.36 ± 23.27	-5.61 (-10.43, -0.79)		
Stratum II						
ezetimibe 10mg + rosuvastatin 10mg	121	101.60 ± 26.67	76.79 ± 32.59	-23.74 (-28.34, -19.14)	-17.46 (-23.92, -10.99)	<0.001
Rosuvastatin 20mg	121	98.44 ± 25.18	90.90 ± 28.78	-6.28 (-10.88, -1.69)		

The secondary endpoints were percent change from baseline in other lipid and lipoprotein parameters and percent change from baseline in LDL-C at Week 6. Ezetimibe 10 mg added to on-going rosuvastatin therapy (5 or 10 mg) significantly lowered total-cholesterol, non-HDL-C and Apo B, compared with doubling of the rosuvastatin dose ($p < 0.001$) and resulted in a significantly greater proportion of patients reaching their LDL-C goal compared with doubling the baseline dose of rosuvastatin (10 mg or 20 mg) (59.4% vs. 30.9%, adjusted odds ratio = 4.5 with a 95% CI of (2.9, 6.9); $p < 0.001$). LDL-C treatment goals were < 1.8 mmol/L for patients at high risk for CHD with AVD and < 2.6 mmol/L for patients at moderately high risk and high risk for CHD without AVD).

Twelve patients discontinued the study early, 6 due to adverse experiences. Treatment groups were similar in the proportion of patients with clinical adverse experiences, serious adverse experiences, drug-related adverse experiences or adverse experiences leading to discontinuation.

Long term studies

There is limited clinical data on the long term effects of ezetimibe and rosuvastatin co-administration, especially at the 10/40 mg dose.

There are no clinical outcome data on cardiovascular morbidity and mortality with ROSUZET. No incremental benefit of ROSUZET on cardiovascular morbidity and mortality over and above that demonstrated for rosuvastatin has been established.

Other Studies

Ezetimibe

Co-adminstration with Fenofibrate

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.

Rosuvastatin

ROSUZET contains rosuvastatin. In a large placebo-controlled clinical trial, the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <3.3 mmol/L (130 mg/dL) and hs-CRP levels ≥2 mg/L. Rosuvastatin significantly reduced the risk of CV events: CV death, non-fatal

myocardial infarction, non-fatal stroke, hospitalisation for unstable angina or an arterial revascularization procedure.

No incremental benefit of ROSUZET on cardiovascular morbidity and mortality over and above that demonstrated for rosuvastatin has been established.

INDICATIONS

Primary Hypercholesterolaemia

ROSUZET is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:

- not appropriately controlled with rosuvastatin or ezetimibe alone; or
- already treated with rosuvastatin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

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

CONTRAINDICATIONS

ROSUZET is contraindicated in patients:

- with known hypersensitivity to any component of this medication
- with myopathy secondary to other lipid lowering agents
- during pregnancy in nursing mothers and in women of childbearing potential, unless they are taking adequate contraceptive precautions (see PRECAUTIONS)
- with active liver disease including unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN) (see PRECAUTIONS)
- in combination with fenofibrate in patients with gall bladder disease
- on fusidic acid therapy (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

Due to the rosuvastatin 40mg component, ROSUZET 10/40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- situations where an increase in rosuvastatin plasma levels may occur (see PHARMACOLOGY, *Pharmacokinetics*, INTERACTIONS WITH OTHER MEDICINES)
- severe renal impairment (CrCl < 30 mL/min)
- Asian patients
- concomitant use of fibrates.

PRECAUTIONS

Treatment with the 10/40 mg Dose

There is limited long term safety data of ROSUZET. Due to the potential increase in rosuvastatin exposure when combined with ezetimibe, risk factors such as hepatic or renal impairment that may increase rosuvastatin exposure and the potential for increased adverse effects at the highest dose (10/40 mg) (e.g. muscle effects, renal impairment and elevated liver enzymes), monitoring of patients on the highest dose of ROSUZET is recommended (See PHARMACOLOGY, *Pharmacokinetics*).

Liver Enzymes

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials.

Liver function tests should be performed before initiation of treatment and periodically thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of ROSUZET is recommended.

ROSUZET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see PHARMACOLOGY: *Characteristics in Patients [Special Populations]* and DOSAGE and ADMINISTRATION). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of ROSUZET (see CONTRAINDICATIONS).

In a pooled analysis of placebo-controlled trials, increases in serum transaminases to >3 times the upper limit of normal occurred in 1.1% of patients taking rosuvastatin versus 0.5% of patients treated with placebo.

In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥ 3 X the upper limit of normal [ULN]) have been observed.

Skeletal Muscle

Rosuvastatin

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.

Uncomplicated myalgia has been reported in rosuvastatin treated patients (see ADVERSE EFFECTS). Creatine kinase (CK) elevations (> 10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values > 10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. In clinical trials, the incidence of myopathy and rhabdomyolysis increased at doses of rosuvastatin above the recommended dosage range (5 to 40 mg). In postmarketing experience, effects on skeletal muscle, e.g. uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with HMG-CoA reductase inhibitors including rosuvastatin. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (≥ 65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy increased at doses of rosuvastatin above the recommended dosage range.

Consequently:
1. ROSUZET should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism.

2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. ROSUZET therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

3. Rosuvastatin 40 mg is reserved only for those patients who are not adequately controlled at the 20 mg dose, considering their level of LDL-C and overall CV risk profile. Similarly, ROSUZET 10/40mg should be reserved for such patients.

4. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies, protease inhibitors, or cyclosporin (see INTERACTIONS WITH OTHER MEDICINES). **The benefit of further alterations in lipid levels by the combined use of ROSUZET with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with ROSUZET and gemfibrozil should generally be avoided. The combination of ROSUZET and other fibrates (except fenofibrate) is not recommended (see DOSAGE AND ADMINISTRATION, INTERACTIONS WITH OTHER MEDICINES and CONTRAINDICATIONS).**

5. The risk of myopathy during treatment with ROSUZET may be increased in circumstances that increase rosuvastatin drug levels (see PHARMACOLOGY: *Characteristics in Patients [Special populations]* and PRECAUTIONS: Impaired renal function).

6. ROSUZET therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, or uncontrolled seizures).

There have been very rare reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

In rosuvastatin trials there was no evidence of increased skeletal muscle effects when rosuvastatin was dosed with any concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with cyclosporin, nicotinic acid, azole antifungals, macrolide antibiotics and fibric acid derivatives including gemfibrozil (see ADVERSE EFFECTS, INTERACTIONS WITH OTHER MEDICINES and DOSAGE AND ADMINISTRATION).

Fusidic acid must not be co-administered with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination (see CONTRAINDICATIONS, ADVERSE EFFECTS and INTERACTIONS WITH OTHER MEDICINES). In patients where the use of systemic fusidic acid is considered essential, ROSUZET treatment should be discontinued throughout the duration of fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. ROSUZET therapy may be re-introduced seven days after the last dose of fusidic acid.

<u>Ezetimibe</u>
In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimibe 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 ezetimibe alone vs 1 of 786 (0.1%) patients administered placebo, and for 1 of 917 (0.1%) patients co-administered ezetimibe and a statin vs 4 of 929 (0.4%) patients administered a statin alone.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported regardless of causality. Most patients who developed rhabdomyolysis were taking a statin prior to initiating ezetimibe. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to agents known to be associated with increased risk of rhabdomyolysis.

Hepatic Insufficiency

Ezetimibe

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

Rosuvastatin

Pharmacokinetic evaluation in subjects with varying degrees of hepatic impairment determined that there was no evidence of increased exposure to rosuvastatin other than in 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

Rosuvastatin

Pharmacokinetic evaluation in subjects with varying degrees of renal impairment, determined that mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin. However, subjects with severe impairment (CrCl < 30 mL/min) had a 3-fold increase in plasma concentration compared to healthy volunteers (see DOSAGE AND ADMINISTRATION).

Renal Effects

Rosuvastatin

The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

Endocrine Effects

Rosuvastatin

Increases in HbA1c and fasting serum glucose levels have been reported with rosuvastatin. Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if ROSUZET is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Caution in prevention of cardiovascular events

Rosuvastatin

The long term safety and efficacy of rosuvastatin treatment in patients commencing treatment with LDL-C < 3.4 mmol/L who have been assessed to be at risk of cardiovascular events have not been established. There is also uncertainty associated with the safety of long term intensive reduction of LDL-C to very low levels. Data are currently available for up to 2 years for the 20 mg dose only. The risk benefit balance for longer term use of rosuvastatin in this population has therefore not been established. The benefits of longer term treatment should be weighed against safety and tolerability risks (see ADVERSE EFFECTS). Clinically significant benefit in using rosuvastatin in

patients without clinically evident cardiovascular disease and who are assessed as having a low risk of cardiovascular events (men >50 and women >60 years of age with hsCRP >2mg/L, but no other cardiovascular disease risk factor) has not been established.

Diabetes Mellitus

Rosuvastatin

Increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin. An increased frequency of diabetes mellitus has been reported with rosuvastatin in patients with risk factors for diabetes mellitus (see ADVERSE EFFECTS).

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, ROSUZET therapy should be discontinued.

Race

Rosuvastatin

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making ROSUZET dosing decisions for Asian patients (see PHARMACOKINETICS and DOSAGE AND ADMINISTRATION).

Age and Sex

Rosuvastatin

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Paediatric Use

Not recommended for use in children.

Use in the Elderly

No dosage adjustment is required for elderly patients. Because there is no specific data in the elderly with this combination and advanced age (≥65 years) is a predisposing factor for myopathy, ROSUZET should be prescribed with caution in the elderly (See PHARMACOLOGY; *Characteristics in Patients [Special Populations]).*

Fibrates

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

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 TRIALS and ADVERSE EFFECTS), co-administration of ROSUZET and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see CONTRAINDICATIONS).

Cyclosporin

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

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

Effects on Fertility
ROSUZET
No studies on the effect on fertility have been conducted with ezetimibe and rosuvastatin in combination.

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

Rosuvastatin
In 1 of 3 monkeys treated with rosuvastatin PO at 30 mg/kg/day for 6 months degenerative changes in the testicular epithelium were seen. The no-effect dose of 10 mg/kg/day was associated with rosuvastatin plasma concentrations (AUC) similar to those expected in humans taking 40 mg rosuvastatin daily. Rosuvastatin had no effect on male or female fertility when administered to rats at PO doses of 50 mg/kg/day (systemic rosuvastatin concentrations (AUC) 4.8-6.6 times those expected in humans). The main human metabolite of rosuvastatin, N-desmethyl rosuvastatin, has not been assessed for activity in rat fertility studies.

Use in Pregnancy [Category D]
Category D is defined as drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

ROSUZET
No studies on the effect on embryofetal development have been conducted with ezetimibe and rosuvastatin in combination.

ROSUZET is contraindicated in Pregnancy. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolaemia. Cholesterol and other products of cholesterol biosynthesis are essential components for foetal development (including synthesis of steroids and cell membranes).

ROSUZET should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential. If the

patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the foetus (see CONTRAINDICATIONS).

Ezetimibe

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. Ezetimibe should be used in pregnancy only if the potential benefit exceeds the potential risk.

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.

Rosuvastatin

Cholesterol and other products of cholesterol biosynthesis are essential components for foetal development, including synthesis of steroids and cell membranes. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis, rosuvastatin is contraindicated during pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

In two series of 178 and 143 cases where pregnant women took a HMG-CoA reductase inhibitor (statin) during the first trimester of pregnancy serious foetal abnormalities occurred in several cases. These included limb and neurological defects, spontaneous abortions and foetal deaths. The exact risk of injury to the foetus occurring after a pregnant woman is exposed to a HMG-CoA reductase inhibitor has not been determined. The current data do not indicate that the risk of foetal injury in women exposed to HMG-CoA reductase inhibitors is high. If a pregnant woman is exposed to a

HMG-CoA reductase inhibitor she should be informed of the possibility of foetal injury and discuss the implications with her pregnancy specialist.

Use in Lactation
No studies in lactating animals have been conducted with the combination of ezetimibe and rosuvastatin.

Studies in rats have shown that ezetimibe and rosuvastatin are excreted in milk. It is not known whether ezetimibe or rosuvastatin is excreted into human breast milk. Therefore, ROSUZET is contraindicated in breastfeeding women (see CONTRAINDICATIONS).

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.

The safety of rosuvastatin while breast-feeding has not been established. A study in rats treated with rosuvastatin showed that unchanged drug and metabolites are excreted in milk at concentrations up to 3 times greater than those in maternal plasma. The results of animal and *in vitro* studies of rosuvastatin are summarised below.

Genotoxicity
ROSUZET
No genotoxicity studies have been conducted with ezetimibe and rosuvastatin in combination.

Ezetimibe
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.

Rosuvastatin
Rosuvastatin showed no evidence for mutagenic activity (*in vitro* assays of reverse mutation in bacterial cells and forward mutation in mammalian cells) or clastogenic activity (*in vitro* assay in mammalian cells and *in vivo* in the mouse micronucleus test). There have been no adequate studies investigating the potential carcinogenic or genotoxic activity of the main human metabolite of rosuvastatin, N-desmethyl rosuvastatin.

Carcinogenicity
Ezetimibe
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 ^{3} 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 500 mg/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.

Rosuvastatin
Oral administration of rosuvastatin for 2 years to rats and mice increased the development of benign uterine stromal polyps in both species and malignant uterine sarcomas and adenosarcomas in rats. Systemic concentrations of rosuvastatin (AUC) at the no-effect dose for benign and malignant uterine tumours in either species were lower than or similar to those expected in humans taking 40 mg/day rosuvastatin.

Animal Studies
Rosuvastatin
Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/day based on AUC comparisons).

Effects on ability to drive and use machines
Ezetimibe
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 ezetimibe may affect some patients' ability to drive or operate machinery. Individual responses to ezetimibe may vary (see ADVERSE EFFECTS).

Rosuvastatin
Pharmacological testing revealed no evidence of a sedative effect of rosuvastatin. From the safety profile, rosuvastatin is not expected to adversely affect the ability to drive or operate machinery.

INTERACTIONS WITH OTHER MEDICINES

Co-administration of ezetimibe with rosuvastatin resulted in a 19% increase in the AUC of rosuvastatin. This small increase is not considered clinically significant (see PRECAUTIONS).

Antacids
Ezetimibe
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.

Rosuvastatin
Simultaneous administration of rosuvastatin and an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

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 ROSUZET and a bile acid binding sequestrant should take place several hours apart. However, efficacy and safety of such combination have not been studied.

Cyclosporin
Ezetimibe
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).

Rosuvastatin
Co-administration of rosuvastatin with cyclosporin resulted in no significant changes in cyclosporin plasma concentration. However, rosuvastatin steady state $AUC_{(0-t)}$ increased up to 7-fold over that seen in healthy volunteers administered the same dose. These increases are considered to be clinically significant and require special consideration in the dosing of ROSUZET (see DOSAGE AND ADMINISTRATION).

Fenofibrate
Ezetimibe

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

Rosuvastatin
Co-administration of fenofibrate with rosuvastatin resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate.

Gemfibrozil
Ezetimibe
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.

Rosuvastatin
Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and $AUC_{(0-t)}$. This increase is considered to be clinically significant (see DOSAGE AND ADMINISTRATION).

Anticoagulants
Ezetimibe
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 ezetimibe added to warfarin. Most of these patients were also on other medications (see PRECAUTIONS).

Rosuvastatin
Co-administration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (> 4, baseline 2-3). In patients taking vitamin K antagonists and rosuvastatin concomitantly, INR should be determined before starting ROSUZET and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on vitamin K antagonists. If the dose of ROSUZET is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.

Cytochrome P450 enzymes
Ezetimibe
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.

Rosuvastatin

In vitro and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Ketoconazole:
Co-administration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin:
Co-administration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. These reductions are not considered clinically significant.

Itraconazole:
Itraconazole (200 mg twice daily for 5 days) resulted in a 39% and 28% increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. These increases are not considered clinically significant.

Fluconazole:
Co-administration of fluconazole (200 mg twice daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. This increase is not considered clinically significant.

Oral contraceptives
Co-administration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively. This increase is not considered clinically significant.

Other medications
Ezetimibe
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.

Rosuvastatin
In clinical studies, rosuvastatin was co-administered with anti-hypertensive agents and anti-diabetic agents. These studies did not produce any evidence of clinically significant adverse interactions.

Digoxin
Co-administration of digoxin with rosuvastatin resulted in no change to digoxin plasma concentrations.

Protease Inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the use of ROSUZET in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating ROSUZET doses in patients treated with protease inhibitors.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Coadministration of this combination may cause increased plasma concentrations of both agents. The mechanism of this interaction (whether it is pharmacodynamics or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with ROSUZET is necessary, ROSUZET treatment should be discontinued throughout the duration of the fusidic acid treatment (see CONTRAINDICATIONS, PRECAUTIONS and ADVERSE EFFECTS).

ADVERSE EFFECTS

Co-administration of ezetimibe and rosuvastatin

Ezetimibe Add-on to On-going Rosuvastatin Therapy
Co-administration of ezetimibe and rosuvastatin has been evaluated for safety in more than 2,409 patients in sponsor-initiated clinical trials and other clinical data from published literature. For full details of adverse effects, please refer to the Product Information for the individual products of ezetimibe and rosuvastatin.

In a 6 week active comparator study (P139V1), 440 subjects taking rosuvastatin (5 mg or 10 mg) were randomized to either rosuvastatin (10 mg or 20 mg) or ezetimibe 10 mg added to rosuvastatin (5 or 10 mg) therapy, equivalent to ROSUZET 10/5mg or 10/10 mg. The co-administration was generally well tolerated (see table below).

The study discontinuation rate due to adverse experiences was 2.3% (n = 5) for the ezetimibe 10 mg + rosuvastatin 5 or 10 mg treatment arm and 0.5% (n = 1) for the rosuvastatin 10 mg or 20mg arm.

Drug-related Adverse Events in any Treatment Group

	Ezetimibe 10 mg + Rosuvastatin 5 or 10 mg (n = 221)	**Rosuvastatin 10 mg or 20mg (n = 219)**
Gastrointestinal disorders		
Abdominal distension	0.45%	0.0%
Abdominal pain	0.45%	0.0%
Constipation	0.90%	0.91%
Dry mouth	0.45%	0.0%
Nausea	0.45%	0.0%
General disorders and administration site conditions		
Asthenia	0.0%	0.46%
Fatigue	0.0%	0.46%
Musculoskeletal and connective tissue disorders		
Arthralgia	0.45%	0.0%
Myalgia	0.90%	0.46%
Skin and subcutaneous tissue disorders		
Allergic dermatitis	0.45%	0.0%
Eczema	0.45%	0.0%
Skin exfoliation	0.0%	0.46%

In this study, the incidence of clinically important elevations in serum transaminases (ALT ³ 3 X ULN, consecutive) was 0.5% (n=1) for patients treated with ezetimibe + rosuvastatin and 0% for patients in the rosuvastatin only treatment group. No patients in either group had clinically significant elevations in AST. Clinically important elevations in creatine kinase (CK ³ 10 X ULN) were seen in 0.5% (n=1) of patients in the rosuvastatin only treatment group and not seen in patients treated with ezetimibe + rosuvastatin.

In another 6 week randomised active comparator study (EXPLORER[3]) in 469 subjects with hypercholesterolemia and a history of CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score > 20%), the incidence of increased ALT at the 10 mg + 40 mg dose was 2.5% (n=6) for ezetimibe + rosuvastatin and 0.4% (n=1) for rosuvastatin alone.

Ezetimibe

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

There were no drug-related adverse experiences reported occurring in ³ 2% of patients taking ezetimibe alone (n = 1691).

The following drug-related adverse experiences were reported occurring in ³ 2% in patients taking ezetimibe co-administered with a statin (n = 1675).

	All Statins (%) N=1676	ezetimibe 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 ezetimibe co-administered with a statin and at a greater incidence than statin administered alone, or in patients taking ezetimibe alone and at a greater incidence than placebo.

Ezetimibe co-administered with a statin:

[3] Ballantyne CM, Weiss R., Moccetti T., Vogt A, Eber B, Sosef F, Duffield E. Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination With Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study). American Journal of Cardiology (2007) 99:5 (673-680).

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; oedema peripheral

Ezetimibe 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

Ezetimibe 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.

Laboratory Values
In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ^{3} 3 X ULN, consecutive) was similar between ezetimibe (0.5 %) and placebo (0.3 %). In co-administration trials, the incidence was 1.3% for patients treated with ezetimibe 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 (^{3} 10 X ULN) in patients treated with ezetimibe 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).

Rosuvastatin

Rosuvastatin is generally well tolerated. The adverse events seen with rosuvastatin are generally mild and transient. In controlled clinical trials less than 4% of rosuvastatin treated patients were withdrawn due to adverse events. This withdrawal rate was comparable to that reported in patients receiving placebo.

Adverse reactions within each body system are listed in descending order of frequency (Very common: ≥10%; common: ≥1% and <10%; uncommon: ≥0.1% and <1%; rare ≥0.01% and <0.1%; very rare: <0.01%). These include the following:

Central Nervous System:	Common:	dizziness
Gastrointestinal:	Common:	constipation, nausea, abdominal pain
	Rare:	pancreatitis
Musculoskeletal:	Common:	myalgia, asthenia
	Rare:	myopathy (including myositis) and rhabdomyolysis
Skin:	Uncommon:	pruritus, rash, urticaria
	Rare:	hypersensitivity reactions including angioedema
Endocrine:	Common:	diabetes mellitus
Miscellaneous:	Common:	headache

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to increase with increasing dose.

Skeletal muscle effects

Rare cases of rhabdomyolysis, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin.
Rhabdomyolysis may be fatal. Examples of signs and symptoms of rhabdomyolysis are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure, cardiac arrhythmia (see CONTRAINDICATIONS, PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

Laboratory effects

As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases, CK, glucose, glutamyl transpeptidase, alkaline phosphatase and bilirubin and thyroid function abnormalities have been observed in a small number of patients taking rosuvastatin. Increases in HbA1c have also been observed in patients treated with rosuvastatin. Proteinuria and microscopic haematuria has been detected by dipstick testing in the clinical trial program in a small number of patients taking rosuvastatin and other HMG-CoA reductase inhibitors at their recommended doses. The proteinuria was mostly tubular in origin and was more frequent in patients on rosuvastatin 40 mg. It was generally transient and not associated with worsening renal function. Although the clinical significance is unknown, dose reduction should be

considered in patients on rosuvastatin 40 mg with unexplained persistent proteinuria and/or haematuria.

Other effects

In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens (see PRECAUTIONS). In rosuvastatin-treated patients, there was no impairment of adrenocortical function.

Post marketing Experience

In addition to the above, the following adverse events have been reported during post marketing experience for rosuvastatin:

Musculoskeletal disorders

Very rare: arthralgia
Frequency unknown: immune-mediated necrotising myopathy

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Haematological disorders

Frequency unknown thrombocytopenia

Hepatobiliary disorders

Rare increased hepatic transaminases
Very rare jaundice, hepatitis
Frequency unknown hepatic failure

Nervous system disorder

Very rare memory loss

Psychiatric disorders

Frequency unknown depression, sleep disorders (including insomnia and nightmares)

Reproductive system and breast disorders

Frequency unknown gynaecomastia

DOSAGE AND ADMINISTRATION

This combination product is not indicated for first-line use.

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

ROSUZET can be administered at any time of the day, with or without food. Each tablet should be taken with water at the same time daily and is not to be chewed or crushed.

Therapy should be individualised according to the target lipid levels, the recommended goal of therapy, and the patient's response. The dose should also take into account the potential risk for adverse reactions (see ADVERSE EFFECTS).

The dosage range of ROSUZET is 10/5 to 10/40 mg once daily. A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of ROSUZET is 10/20 mg once per day.

A dose of 10/40 mg once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 10/20 mg once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. It is recommended that the 10/40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 10/40 mg must not be exceeded in any patient.

Specialist supervision should be considered when the dose of ROSUZET is titrated to 10/40 mg.

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

Use in Paediatric Patients
Not recommended for use in children.

Hepatic Insufficiency
There may be increased exposure to rosuvastatin in patients receiving the combination. The lowest effective dose should be used and regular monitoring for adverse effects should be performed. No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment 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 PHARMACOLOGY: *Characteristics in Patients [Special Populations]*).

Renal Insufficiency
There may be increased exposure to rosuvastatin in patients receiving this combination. The lowest effective dose should be used and regular monitoring for adverse effects should be performed. No dosage adjustment is required for patients with mild to moderate renal impairment. For patients with severe renal impairment (CLcr<30 mL/min/1.73m^2) not on dialysis the dose of ROSUZET should be started at 10/5 mg once daily and not exceed 10/10 mg once daily (see PRECAUTIONS).

The reporting rate for serious renal events in post-marketing use of rosuvastatin alone is higher at the 40 mg dose. An assessment of renal function is therefore recommended during routine follow-up of patients treated with the fixed-dose combination ROSUZET at a dose of 10/40 mg.

Dosage in Asian patients
Initiation of therapy with ROSUZET 10/5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 10/5 mg, 10/10 mg or 10/20 mg once daily (see PHARMACOKINETICS and PRECAUTIONS).

Dosage in patients taking other drugs

Cyclosporin

In patients taking cyclosporin, ROSUZET dosage should be limited to 10/5 mg once daily (see INTERACTIONS WITH OTHER MEDICINES).

Gemfibrozil
Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant rosuvastatin and gemfibrozil (see INTERACTIONS WITH OTHER MEDICINES). If ROSUZET is used in combination with gemfibrozil, the dose should be limited to 10/10 mg once daily.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

No specific treatment of overdosage with ROSUZET can be recommended. In the event of an overdose, symptomatic and supportive measures should be employed. In symptomatic patients, monitor serum creatinine, BUN, creatinine phosphokinase and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients.

Ezetimibe
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 ezetimibe 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.

Rosuvastatin
There is no specific treatment for overdose. In case of overdose treatment should be supportive and symptomatic. Haemodialysis is unlikely to be of benefit.

PRESENTATION AND STORAGE CONDITIONS

ROSUZET 10mg/5mg: contains 10 mg ezetimibe and 5 mg rosuvastatin (as calcium). It is a circular, uncoated, bilayer tablet with one white to off white layer debossed with “C1” and other plain white to off white layer

ROSUZET 10mg/10mg: contains 10 mg ezetimibe and 10 mg rosuvastatin (as calcium). It is a circular, uncoated, bilayer tablet with one white to off white layer debossed with “C2” and other plain white to off white layer

ROSUZET 10mg/20mg: contains 10 mg ezetimibe and 20 mg rosuvastatin (as calcium). It is a circular, uncoated, bilayer tablet with one white to off white layer debossed with “C3” and other plain white to off white layer

ROSUZET 10mg/40mg: contains 10 mg ezetimibe and 40 mg rosuvastatin (as calcium). It is a circular, uncoated, bilayer tablet with one white to off white layer debossed with "C4" and other plain white to off white layer

Available as 9, 30 tablet Adherence blister (PVC/aclar/aluminium) packs and 10, 30 tablet Traditional carton blister (aluminium/OPA/aluminium/PVC) packs.

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1 Building A
26 Talavera Road
Macquarie Park NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

2 September 2014

DATE OF MOST RECENT AMENDMENT

N/A

Tracer Number: 0653H-AUS-2014-009615