PRODUCT INFORMATION

ATOZET®

[ezetimibe, atorvastatin (as calcium trihydrate)]

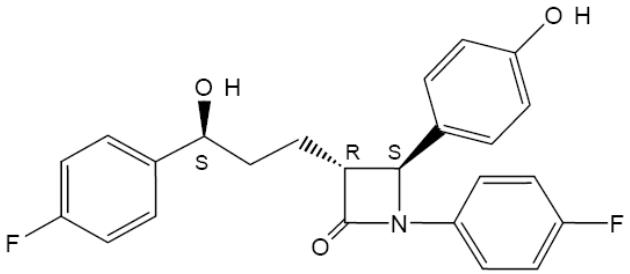
ATOZET 10 mg/10 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 10 mg
ATOZET 10 mg/20 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 20 mg
ATOZET 10 mg/40 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 40 mg
ATOZET 10 mg/80 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 80 mg

NAME OF THE MEDICINE

ATOZET is a film-coated tablet containing ezetimibe 10mg and atorvastatin 10, 20, 40 or 80 mg.

Ezetimibe

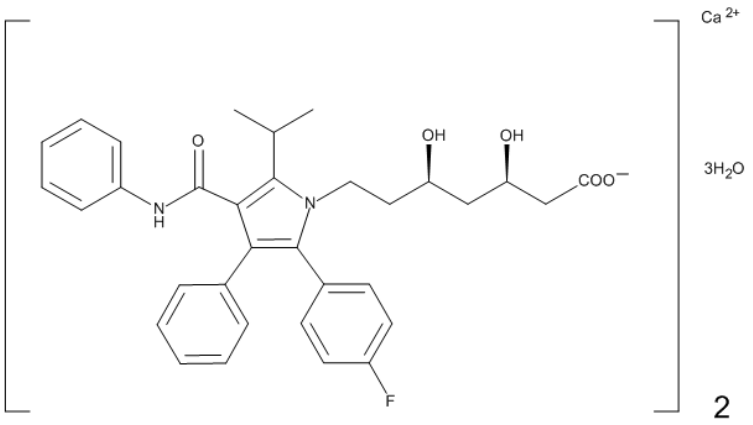
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone. The CAS registry number is 163222-33-1. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Atorvastatin

Atorvastatin is [*R*-(*R**,*R**)]-2-(4-fluorophenyl)-b, d-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl] -1*H*-pyrrole -1-heptanoic acid, calcium salt (2:1) trihydrate.

The CAS registry number is 344423-98-9. The molecular formula of atorvastatin calcium trihydrate is $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$. The molecular weight of atorvastatin calcium trihydrate 1209.36. Its structural formula is:



DESCRIPTION

ATOZET is available for oral use as tablets containing 10 mg of ezetimibe and: 10.9 mg of atorvastatin calcium trihydrate, equivalent to 10 mg of atorvastatin (ATOZET 10 mg/10 mg); 21.7 mg of atorvastatin calcium trihydrate, equivalent to 20 mg of atorvastatin (ATOZET 10 mg/20 mg); 43.4 mg of atorvastatin calcium trihydrate, equivalent to 40 mg of atorvastatin (ATOZET 10 mg/40 mg); or 86.8 mg of atorvastatin calcium trihydrate, equivalent to 80 mg of atorvastatin (ATOZET 10 mg/80 mg).

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.

Atorvastatin calcium trihydrate is a white or almost-white powder that is soluble in dimethyl sulfoxide. The degree of solubility in water, ethanol and methylene chloride is very slightly soluble to practically insoluble.

Each film-coated tablet of ATOZET contains the following inactive ingredients: calcium carbonate, silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone and sodium lauryl sulfate.

The film coating contains: hypromellose, macrogol 8000, titanium dioxide and purified talc.

PHARMACOLOGY

Mechanism of action

ATOZET (ezetimibe/atorvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. ATOZET contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. Together these distinct mechanisms reduce total-C, LDL-C, Apo B, TG, and non-HDL-C, and increase HDL-C beyond either treatment alone, through dual inhibition of cholesterol absorption and synthesis.

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.

Ezetimibe

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. 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, ethinyloestradiol, or the fat soluble vitamins A and D.

Atorvastatin

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. Low density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a marked and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Atorvastatin reduces total-C, LDL-C, and Apo B in both normal volunteers and in patients with homozygous and heterozygous familial hypercholesterolaemia (FH), non-familial forms of hypercholesterolaemia, and mixed dyslipidaemia. Atorvastatin also reduces very low density lipoprotein cholesterol (VLDL-C) and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, Apo B and TG, and increases HDL-C in patients with isolated hypertriglyceridaemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinaemia. In animal models, atorvastatin limits the development of lipid-enriched atherosclerotic lesions and promotes the regression of pre-established atheroma.

Atorvastatin and its metabolites are responsible for pharmacological activity in humans. The liver is its primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dose rather than systemic drug concentration correlates better with LDL-C reduction. Individualisation of drug dose should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics

ATOZET has been shown to be bioequivalent at the high and low end of dosage to coadministration of corresponding doses of ezetimibe and atorvastatin tablets. Bioequivalence at the mid dose ranges has been extrapolated.

The effects of a high-fat meal on the pharmacokinetics of ezetimibe and atorvastatin when administered as ATOZET tablets are comparable to those reported for the individual tablets.

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 ezetimibe 10 mg tablets.

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.

Atorvastatin

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. A constant proportion of atorvastatin is absorbed intact. The absolute bioavailability is 14%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution

The mean volume of distribution of atorvastatin is about 400 litres. Atorvastatin is ≥98% bound to plasma proteins. A RBC/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see PRECAUTIONS).

Metabolism

In humans, atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives. In vitro inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Characteristics in Patients (Special Populations)

Paediatric Patients

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.

Atorvastatin

Pharmacokinetic studies have not been conducted in the paediatric population.

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.

Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Lipid effects are comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender

Ezetimibe

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

Atorvastatin

Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men; however, there is no clinically significant difference in lipid effects with atorvastatin between men and women.

Race

There are no pharmacokinetic data on the co-administration of ezetimibe and atorvastatin in non-Caucasians.

Ezetimibe

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

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).

Atorvastatin

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (see CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 to be 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.

Atorvastatin

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Haemodialysis

Haemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Despite the expected cholesterol changes, no cardiovascular benefit with atorvastatin has been demonstrated in haemodialysis patients. ATOZET has not been studied in this population.

CLINICAL TRIALS

In controlled clinical studies, ATOZET (co-administration of ezetimibe and atorvastatin) significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

No incremental benefit of ATOZET on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

Primary Hypercholesterolaemia

ATOZET

Ezetimibe Initiated Concurrently with Atorvastatin

In a multicentre, double-blind, placebo-controlled, clinical study (P0692) in patients with hyperlipidaemia, 628 patients (260 male, 368 female) were treated for up to 12 weeks and 246 for up to an additional 48 weeks. Patients were 18 to 86 years of age, with baseline LDL-C concentrations between 130 to 253 mg/dL (3.37 to 6.55 mmol/L) (mean baseline LDL-C ranged from 175 and 184 mg/dL [4.53 and 4.77 mmol/L] across treatment groups). Sixty-three percent had risk factors or a history of cardiovascular disease. Patients were randomised

to receive placebo, ezetimibe (10 mg), atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/10, 10/20, 10/40, and 10/80) in the 12-week study. After completing the 12-week study, eligible patients were assigned to co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/10-10/80) or atorvastatin (10-80 mg/day) for an additional 48 weeks (See CLINICAL TRIALS, *Long term studies*, P2154).

Eight percent of subjects discontinued treatment early, 5% were due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation.

Patients receiving all doses of ATOZET were compared to those receiving all doses of atorvastatin. The primary endpoint was percent change from baseline in direct LDL-C at study endpoint (12 weeks). Secondary endpoints were percent change from baseline in calculated LDL-C, TC, TG, HDL-C and Apo B at endpoint. ATOZET lowered total C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone. (See Table 1)

Table 1
Response to ATOZET in Patients with Primary Hyperlipidaemia (ITT analysis)
(Mean[a] % change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Pooled data (All ATOZET doses)[c]	255	-41	-56	-45	-33	+7	-52
Pooled data (All atorvastatin doses)[c]	248	-32	-44	-36	-24	+4	-41
Ezetimibe 10 mg	65	-14	-20	-15	-5	+4	-18
Placebo	60	+4	+4	+3	-6	+4	+4
ATOZET by dose							
10/10	65	-38	-53	-43	-31	+9	-49
10/20	62	-39	-54	-44	-30	+9	-50
10/40	65	-42	-56	-45	-34	+5	-52
10/80	63	-46	-61	-50	-40	+7	-58
Atorvastatin by dose							
10 mg	60	-26	-37	-28	-21	+6	-34
20 mg	60	-30	-42	-34	-23	+4	-39
40 mg	66	-32	-45	-37	-24	+4	-41
80 mg	62	-40	-54	-46	-31	+3	-51

a For triglycerides, median % change from baseline
b Baseline – on no lipid-lowering drug
c ATOZET pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, non-HDL-C, and significantly increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

The changes in lipid endpoints after an additional 48 weeks of treatment with ATOZET (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.

Ezetimibe Added to Stable Atorvastatin Therapy

In a multicentre, double-blind, placebo-controlled, 8-week study (P2173/2246), 769 (443 male, 326 female) patients aged 22 to 85 years with hypercholesterolaemia (baseline LDL-C ranged from 71 to 455 mg/dL [1.84 to 11.78 mmol/L]; mean baseline LDL-C 138 to 139 mg/dL [3.57 to 3.60 mmol/L] across the treatment groups), 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 ezetimibe 10 mg or placebo in addition to their on-going statin therapy. Sixty-eight percent of subjects had CHD, diabetes and/or CHD equivalent disease with LDL-C ≥ 100 mg/dL (≥2.59 mmol/L).

Fifty-three subjects discontinued study treatment early, 34 were due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or the reasons for discontinuation.

The primary efficacy endpoint was the difference in mean percent change in LDL-C between the treatment groups. The secondary endpoints included the percentage of subjects who achieved NCEP ATP II target LDL-C levels. Endpoints were analysed for a modified ITT population (all subjects who received randomised treatment and had at least one post-baseline value).

Three percent of subjects discontinued treatment early due to adverse events in each treatment group.

In the subgroup of 308 patients with hypercholesterolaemia already receiving atorvastatin monotherapy and not at LDL-C goal at baseline (~83%), significantly more patients randomised to ezetimibe co-administered with atorvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo co-administered with atorvastatin, 72% vs. 27%; the analysis was post-hoc. Ezetimibe added to atorvastatin therapy lowered LDL-C significantly more than placebo added to atorvastatin therapy, 25% vs. 4%. In addition, ezetimibe added to atorvastatin therapy significantly decreased total-C, Apo B, and TG compared with placebo added to atorvastatin therapy.

After 8 weeks of treatment, 730 patients had their blinded ezetimibe or placebo withdrawn and were continued on their stable statin therapy for another 6 weeks (P2173R). Twenty-one subjects discontinued treatment during the reversibility phase. Lipid parameters were observed to return to their pre-treatment values during this period, without any evidence of rebound.

Another double-blind, randomised, placebo-controlled study (P040) evaluated the effect of ezetimibe 10 mg/day added to ongoing statin therapy vs. continued statin therapy alone (at unchanged dose) in 3030 patients (52% male) mean age 62 years and with hypercholesterolemia who were not at their NCEP ATP III Target LDL-C level. Mean baseline LDL-C was 129 mg/dL (3.34 mmol/L). Approximately 78% of patients had CHD or risk equivalent. Adverse experiences resulting in discontinuation occurred in 2.1% of the statin monotherapy groups and in 1.4% of the ezetimibe/statin groups.

The primary outcome was percent change in LDL-C from baseline at week 6. In the subgroup of patients receiving atorvastatin (n=1194) the addition of ezetimibe to atorvastatin produced a reduction of 27.2% in LDL-C at week 6 (relative to the on-statin baseline) compared to 4.2% for placebo, a difference of 23.0% (Modified ITT analysis – excluded patients who had adverse clinical or laboratory experiences, lost to follow-up,

protocol deviations, withdrawn consent, discontinued for other reasons and missing LDL-C measurements).In addition, a greater number of patients in the active ezetimibe group achieved their NCEP ATP III Target Goal for LDL-C, 23.9% for atorvastatin alone vs. 74.6% for ezetimibe + atorvastatin (secondary outcome).

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

A multicentre, double-blind, controlled, 14-week study (P00693) was conducted in 621 patients (330 male, 291 female) with heterozygous familial hypercholesterolemia (HeFH), coronary heart disease (CHD), or multiple cardiovascular risk factors (≥2), adhering to an National Cholesterol Education Program (NCEP) Step I or stricter diet. Patients were 18 to 82 years of age with baseline LDL-C of 117 to 466 mg/dL (3.03 to 12.07 mmol/L) (mean LDL-C : 186 mg/dL and 187 mg/dL [4.82 mmol/L and 4.84 mmol/L] for patients receiving co-administered ezetimibe and atorvastatin 10/10 and atorvastatin 20 mg respectively). Fifty-eight percent of patients were diagnosed with HeFH and the majority of subjects (87%) had risk factors or a family history of cardiovascular disease.

All patients received atorvastatin 10 mg for a minimum of 4 weeks prior to randomisation. Patients were then randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ATOZET 10/10) or atorvastatin 20 mg/day monotherapy. Patients who did not achieve their LDL-C target goal after 4 and/or 9 weeks of randomised treatment were titrated to double the atorvastatin dose. There were 181 patients in the atorvastatin monotherapy treatment arm (all doses) and 181 in the co-administration arm (all doses).

Nine percent of subjects discontinued treatment early, 4% due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation.

Efficacy analyses were carried out on an ITT basis.

The primary endpoint was proportion of subjects achieving target LDL-C levels of ≤ 2.59 mmol/L (≤ 100 mg/dL) at week 14. A higher proportion of subjects on ATOZET (22%), than on atorvastatin alone (7%) achieved target LDL-C levels of ≤ 2.59 mmol/L (100 mg/dL) at week 14 ($p<0.01$).

The secondary endpoints included mean percent change from baseline in LDL-C and proportion of subjects achieving target LDL-C levels at week 4. ATOZET 10/10 was significantly more effective than doubling the dose of atorvastatin to 20 mg in further reducing total-C, LDL-C, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (See Table 2.) In addition, at week 4 significantly more patients receiving ATOZET 10/10 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 20 mg, 12% vs. 2%. The baseline mean LDL-C levels for patients receiving ATOZET 10/10 and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

Table 2
Response to ATOZET after 4 Weeks in Patients with CHD or Multiple Cardiovascular Risk Factors and an LDL-C ≥130 mg/dL (≥3.37 mmol/L) (Modified ITT analysis)
(Mean* % Change from Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	HDL-C	TG*	Non-HDL-C
ATOZET 10/10	305	-17‡	-24‡	+2	-9‡	-22‡
Atorvastatin 20 mg	316	-6	-9	+1	-4	-8

*For triglycerides, median % change from baseline
†Patients on atorvastatin 10 mg, then switched to ATOZET 10/10 or titrated to atorvastatin 20 mg
‡p<0.05 for difference with atorvastatin

The Titration of Atorvastatin Versus Ezetimibe Add-On to Atorvastatin in Patients with Hypercholesterolaemia (TEMPO) study, a multicentre, double-blind, controlled, 6-week study (P079), included 184 patients (55% male) mean age 57 (range 24 to 78 years) with an LDL-C level ≥2.6 mmol/L and ≤4.1 mmol/L (≥100 mg/dL and ≤160 mg/dL), mean baseline LDL-C of 3.08 mmol/L (118.9 mg/dL) and at moderate high risk for coronary heart disease (CHD). All patients received atorvastatin 20 mg for a minimum of 4 weeks prior to randomisation. Patients not at the optional NCEP ATP III LDL-C level (<2.6 mmol/L [<100 mg/dL]) were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ATOZET 10/20) or atorvastatin 40 mg for 6 weeks. Thirteen patients discontinued study treatment; 2 were due to adverse events.

The primary endpoint was percent change from baseline LDL-C at week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). ATOZET 10/20 was significantly more effective than doubling the dose of atorvastatin to 40 mg in further reducing total-C, LDL-C, Apo B and non-HDL-C. Results for HDL-C and TG between the two treatment groups were not significantly different (See Table 3). In addition, significantly more patients receiving ATOZET 10/20 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 40 mg, 84% vs. 49% (secondary endpoint).

Table 3
Response to ATOZET in Patients with Primary Hypercholesterolaemia (Modified ITT analysis)
(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ATOZET 10/20	92	-20[c]	-31[c]	-21[c]	+3	-18	-27[c]
Atorvastatin 40 mg	92	-7	-11	-8	+1	-6	-10

a For triglycerides, median % change from baseline
b Patients on atorvastatin 20 mg, then switched to ATOZET 10/20 or titrated to atorvastatin 40 mg
c p<0.05 for difference with atorvastatin

The Ezetimibe Plus Atorvastatin Versus Atorvastatin Titration in Achieving Lower LDL-C Targets in Hypercholesterolemic Patients (EZ-PATH) study, a multicentre, double-blind, controlled, 6-week study (P090), included 556 (60% male) patients with a mean age of 61 years and an LDL-C level ≥1.8 mmol/L and ≤4.1 mmol/L (≥70 mg/dL and ≤160 mg/dL) and at high risk for coronary heart disease (CHD). All patients received atorvastatin 40 mg for a minimum of 4 weeks prior to randomisation. Patients not at the optional NCEP ATP III LDL-C level <1.8 mmol/L (<70 mg/dL) were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ATOZET 10/40) or atorvastatin 80 mg for 6 weeks. Four patients in the ezetimibe/atorvastatin group and 6 patients in the atorvastatin monotherapy group experienced an adverse event that lead to discontinuation of the study treatment.

The primary outcome was mean percent change from baseline in LDL-C at week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). ATOZET 10/40 was significantly more effective than doubling the dose of atorvastatin to 80 mg in further reducing total-C, LDL-C, Apo B, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (See Table 4). In addition, significantly more patients receiving ATOZET 10/40 attained LDL-C <1.8 mmol/L (<70 mg/dL) compared to those receiving atorvastatin 80 mg, 74% vs. 32% (secondary endpoint).

Table 4
Response to ATOZET in Patients with Primary Hypercholesterolaemia (Modified ITT analysis)
(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ATOZET 10/40	277	-17[c]	-27[c]	-18[c]	0	-12[c]	-23[c]
Atorvastatin 80 mg	279	-7	-11	-8	-1	-6	-9

a For triglycerides, median % change from baseline
b Patients on atorvastatin 40 mg, then switched to ATOZET 10/40 or titrated to atorvastatin 80 mg
c $p<0.05$ for difference with atorvastatin

A multicentre, randomised, double-blind, parallel arm, 12-week study (P112) evaluated the lipid altering efficacy and safety of the addition of ezetimibe 10 mg to atorvastatin 10 mg, as compared to doubling the dose of atorvastatin from 10 mg to 20 mg and followed by further up-titration from atorvastatin 20 to 40 mg. The 1053 patients (53.3% female) were 65 years of age and older (mean age 71.2; range 65 to > 90 years), at high risk for CHD with or without diagnosed atherosclerotic vascular disease (AVD) who had not reached an LDL-C level of <70 mg/dL (1.81 mmol/L) or <100 mg/dL (2.59 mmol/L), respectively, and on atorvastatin 10 mg/day. Mean baseline LDL-C levels were 102 mg/dL (2.64 mmol/L). Twenty-two patients (2%) discontinued treatment due to an adverse event.

The primary endpoint was percent change in LDL-C from baseline to week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). Ezetimibe added to atorvastatin (equivalent to ATOZET 10/10) significantly reduced LDL-C from baseline after 6 weeks of treatment compared with doubling the dose of atorvastatin from 10 to 20 mg (-26.7% vs -12.8%; $p<0.001$). Additionally, treatment with ATOZET 10/10 resulted in a significantly greater percentage of patients achieving LDL-C <100 mg/dL (2.59 mmol/L) for high risk patients without AVD and <70 mg/dL (1.81 mmol/L) for high risk patients with AVD after 12 weeks of treatment, compared to the group that had atorvastatin increased to 40 mg at week 6 (49.4% vs. 39.3%, $p<0.001$).

Switching Study

In a multicentre, double-blind, controlled, 12-week, 2-phase study (P162), 1539 high-cardiovascular-risk patients, with a LDL-C level between 2.6 mmol/L and 4.1 mmol/L (100 and 160 mg/dL) at baseline, on atorvastatin 10 mg daily were randomised to one of three treatment groups: two of which were atorvastatin 20 mg or ATOZET 10/10. After 6 weeks of

treatment (Phase I), based on a random allocation schedule established at the start of Phase I, patients taking atorvastatin 20 mg who failed to achieve a LDL-C level < 2.6 mmol/L (100 mg/dL) were switched to either atorvastatin 40 mg or ATOZET 10/20 for 6 weeks (Phase II). Reductions in LDL-C and comparisons between the ATOZET group and other treatment groups studied are shown in Table 5.

Table 5

Response to ATOZET (Co-administration of Ezetimibe and Atorvastatin) in High-Risk Patients with a LDL-C Level Between 2.6 mmol/L and 4.1 mmol/L (100 and 160 mg/dL) on Atorvastatin 10 mg Daily at Baseline

Treatment	**N**	**Percent Change from Baseline**[†]					
		Total-C	LDL-C	Apo B	TG[‡]	HDL-C	Non-HDL-C
Phase I Switched from atorvastatin 10 mg							
ATOZET 10/10	120	-13.5	-22.2	-11.3	-6.0	+0.6	-18.3
Atorvastatin 20 mg	480	-6.4[§]	-9.5[§]	-6.0[¶]	-3.9	-1.1	-8.1[§]
Phase II Switched from atorvastatin 20 mg							
ATOZET 10/20	124	-10.7	-17.4	-9.8	-5.9	+0.7	-15.1
Atorvastatin 40 mg	124	-3.8[Þ]	-6.9[Þ]	-5.4	-3.1	+1.7	-5.8[Þ]

[†] M-Estimates (based on the method of Huber; 95% CI and p-value were obtained from fitting a robust Regression model with terms for treatment and baseline)
[‡] Geometric mean percent changes from baseline in TG were calculated based on back-transformation via exponentiation of the model-based least square (LS) means and expressed as (geometric mean – 1) multiplied by 100
[§] p<0.001 versus ATOZET 10/10
[¶] p<0.01 versus ATOZET 10/10
[Þ] p<0.001 versus ATOZET 10/20

Table 5 does not contain data comparing the effects of ATOZET 10/10 or 10/20 to doses higher than atorvastatin 40 mg.

Long term studies

A 12-month, blinded comparator study (P2154) enrolled 246 (101 male, 145 female) subjects who had completed study P0692. Patients in this follow-on study were aged from 26 to 86 years, with primary hypercholesterolaemia. Mean baseline LDL-C was 184.6 and 180.6 mg/dL (4.78 and 4.68 mmol/L) in the atorvastatin monotherapy and co-administration groups respectively. A greater proportion of subjects in the monotherapy group had a medical history

or physical finding of cardiovascular disease (31% vs. 19%) and were hypertensive (42% vs. 34%) compared to the co-administration group. Forty-one subjects discontinued treatment; 22 discontinued due to adverse events (3/45 in the monotherapy group and 19/201 in the co-administration group).

Patients were initially dosed with either double-blind ezetimibe 10 mg or matching placebo co-administered with open-label atorvastatin 10 mg once daily in the morning. After at least 6 weeks, the atorvastatin dose could be titrated up incrementally to a maximum of 80 mg once daily to achieve the subject's NCEP ATP II target LDL-C level. Efficacy evaluations were performed on all subjects in the follow-up study who had at least one post-baseline lipid measurement (modified ITT). Overall, co-administration of ezetimibe and atorvastatin (equivalent to ATOZET) reduced LDL-C levels during this 12-month study significantly more than atorvastatin monotherapy. At week 6 (the first time point assessed), LDL-C was reduced from baseline by approximately 37% in the atorvastatin monotherapy group and by approximately 53% in the ATOZET group. The LDL-C-lowering effect was seen by six weeks of treatment and maintained during the 12-month double-blind study period.

A 12-month, open-label study (P1418) was conducted in patients with HeFH, known CHD or multiple cardiovascular risk factors (≥2) who were not controlled by a starting dose of atorvastatin 10 mg and had successfully completed a 14-week double-blind efficacy and safety study (P00693). Four hundred and thirty-two hypercholesterolaemic patients (56% male) with mean age 52 years (range 18 to 82 years) and mean baseline LDL-C 187 mg/dL (4.84 mmol/L) received open-label ezetimibe 10 mg co-administered with atorvastatin 10 mg (equivalent to ATOZET 10/10) at the beginning of the study, with up titration of atorvastatin to reach target LDL-C. Eighty-nine percent of patients had a cardiovascular risk factor or family history of cardiovascular disease. Approximately 38% had a history of hypertension and 26% had angina pectoris. Thirty-four subjects discontinued from the follow-on study, 12 due to adverse events.

Efficacy evaluations were carried out on all subjects in the follow-on study who had at least one post-baseline lipid measurement (modified ITT). Over the 12-month study period, ATOZET 10/10-10/80 was effective in achieving and maintaining a reduction in LDL-C. The mean LDL-C value at study end was reduced by 30% from the parent study baseline. Reductions were noted as of Month 1, were slightly greater at Month 3 and were maintained at similar levels throughout the study period. Commensurate reductions in TC were observed, and reductions in TG, and an increase in HDL-C, were also noted over time.

Homozygous Familial Hypercholesterolaemia (HoFH)

A double-blind, randomised, 12 week study (P1030) was performed in 50 patients (21 male, 29 female, aged 11 to 74 years of age) with a clinical and/or genotypic diagnosis of HoFH. Baseline LDL-C concentrations ranged from 116 to 652 mg/dL (3.00 to 16.89 mmol/L) (mean: 346 mg/dL [8.96 mmol/L] in the monotherapy group; 321 mg/dL [8.31 mmol/L] in the co-administration group). Approximately 74% of subjects had known family history of coronary artery disease and approximately 16% had some degree of hypertension at baseline. Twenty-five subjects received concomitant apheresis or plasmapheresis. Two subjects discontinued treatment early due to adverse events considered to be unrelated to study treatment.

Data were analysed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline (ITT). The primary endpoint was the percent change from baseline in direct LDL-C concentration at week 12. Increasing the dose of atorvastatin from 40 to 80 mg (n=12)

produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/40 and 10/80 pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg. In those patients co-administered ezetimibe and atorvastatin equivalent to ATOZET (10/80 mg, n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg was produced.

After completing the 12 week study, eligible patients (n=35), who were receiving atorvastatin 40 mg at baseline, were assigned to co-administered ezetimibe and atorvastatin equivalent to ATOZET 10/40 for up to an additional 24 months (P1417). Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg. One patient discontinued treatment due to a drug related adverse event. At the end of the 24 months, ATOZET (10/40 and 10/80 mg pooled) produced a reduction of 18% in LDL-C that was consistent with that seen in the 12-week study (modified ITT analysis – included patients who completed 24 months of treatment).

Ezetimibe

In two multicentre, double-blind, placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, race and baseline LDL-C. In addition, ezetimibe 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.

Atorvastatin

Prevention of Cardiovascular Disease

In a placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin 10 mg on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients, 40-80 years old, with TC levels ≤251 mg/dL (6.5 mmol/L) and at least three cardiovascular risk factors. Patients were followed for a median duration of 3.3 years. Atorvastatin 10 mg significantly (p=0.0005) reduced the rate of coronary events (either fatal coronary heart disease [46 events in the placebo group vs. 40 events in the atorvastatin group] or nonfatal MI [108 events in the placebo group vs. 60 events in the atorvastatin group]) by 36% (based on incidences of 1.9% for atorvastatin vs. 3.0% for placebo).

Although this difference was statistically significant for the whole trial population, this difference was not statistically significant in specified subgroups such as diabetes, patients with left ventricular hypertrophy (LVH), previous vascular disease or metabolic syndrome.

There was no statistically significant reduction in the rate of total mortality, cardiovascular mortality or heart failure in the atorvastatin treated group compared to placebo.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ATOZET.

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.

INDICATIONS

Primary Hypercholesterolaemia

ATOZET 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 atorvastatin or ezetimibe alone; or
- already treated with atorvastatin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

ATOZET is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication.
- Myopathy secondary to other lipid lowering agents
- Active liver disease or unexplained persistent elevations of serum transaminases (see PRECAUTIONS).
- Pregnancy and lactation (See PRECAUTIONS). Women of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.
- ATOZET in combination with fenofibrate is contraindicated in patients with gall bladder disease.
- Concomitant use with fusidic acid (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

No incremental benefit of Atozet on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

Liver Enzymes

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin.

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2, 0.2, 0.6, and 2.3% for 10, 20, 40, and 80mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced,

or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

In controlled clinical studies, the incidence of consecutive elevations (³ 3 X the upper limit of normal [ULN]) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled co-administration trials in patients receiving ezetimibe with atorvastatin, the incidence of consecutive elevations (³ 3 X ULN) in hepatic transaminase levels was 0.6% for patients treated with ezetimibe administered with atorvastatin (See ADVERSE EFFECTS).

Liver function tests should be performed before the initiation of treatment and periodically thereafter. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

ATOZET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of ATOZET (see CONTRAINDICATIONS).

Hepatic Insufficiency

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

Skeletal Muscle

Ezetimibe

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.

Atorvastatin

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporin and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatinine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. ATOZET therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, azole antifungals, colchicine, or hepatitis-C protease inhibitors (e.g.telaprevir, boceprevir) (see INTERACTIONS WITH OTHER MEDICINES). Physicians considering combined therapy with ATOZET and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, colchicine, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of ATOZET should be considered when taken concomitantly with the aforementioned drugs. (See DOSAGE ADMINISTRATION, Use in Combination with Other Medicinal Compounds) Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 6 (see DOSAGE AND ADMINISTRATION, Cyclosporin, Clarithromycin, Itraconazole, or Certain Protease Inhibitors, and INTERACTIONS WITH OTHER MEDICINES, CYP3A4Interactions).

Table 6
Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations for ATOZET
Cyclosporin, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir), gemfibrozil	Avoid ATOZET.
Other fibrates (except fenofibrate), fusidic acid	Not recommended with ATOZET
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir), hepatitis C protease inhibitor (boceprevir)	Do not exceed 10/20 mg ATOZET daily.
HIV protease inhibitor (nelfinavir)	Do not exceed 10/40 mg ATOZET daily.

* Use with caution and with the lowest dose necessary

There have been reports of rhabdomyolysis (including some fatalities) in patients receiving concomitant fusidic acid and statins (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES). In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of the fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

ATOZET therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Fibrates

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied. Therefore, co-administration of ATOZET and fibrates is 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 TRIALS and ADVERSE EFFECTS sections), co-administration of ATOZET and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see CONTRAINDICATIONS).

Cyclosporin

In patients taking cyclosporine, therapy with ATOZET should be avoided (See Table 6, INTERACTIONS WITH OTHER MEDICINES and DOSAGE AND ADMINISTRATION).

Anticoagulants

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

Haemorrhagic Stroke

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed a higher incidence of haemorrhagic stroke in patients on atorvastatin 80 mg (55/2365, 2.3%) compared to placebo (33/2366, 1.4%), (p=0.02). Throughout the study, all cause mortality was numerically higher in the atorvastatin arm than the placebo arm. At study end all cause mortality was 9.1% on atorvastatin vs. 8.9 % on placebo.

The increased risk of haemorrhagic stroke was observed in patients who entered the study with prior haemorrhagic stroke (15.6% for atorvastatin vs. 4.2 % for placebo, HR 4.06; 95% CI 0.84-19.57) or prior lacunar infarct (2.8% for atorvastatin vs. 0.6% for placebo, HR 4.99; 95%CI 1.71-14.61). All cause mortality was also increased in these patients with prior haemorrhagic stroke (15.6% for atorvastatin vs. 10.4% for placebo) or prior lacunar infarct (10.9% for atorvastatin vs. 9.1% for placebo). The potential risk of haemorrhagic stroke should be carefully considered before initiating treatment with ATOZET in patients with recent (1-6 months) stroke or TIA.

In 68% of patients who entered the study with neither a haemorrhagic stroke nor lacunar infarct, the risk of haemorrhagic stroke on atorvastatin vs. placebo was 2% vs. 1.8 % (large vessel), 1.7% vs. 1.6 % (TIA), 1.6% vs. 1.7 % (unknown cause).

Endocrine Function

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if ATOZET is administered concomitantly with other drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see ADVERSE EFFECTS). 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, ATOZET therapy should be discontinued.

Effects on Fertility

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.

Atorvastatin

The effects of atorvastatin on spermatogenesis and human fertility have not been investigated in clinical studies. Dietary administration of 100 mg atorvastatin/kg/day to rats caused a decrease in spermatid concentration in the testes, a decrease in sperm motility and an increase in sperm abnormalities. Similar effects, however, were not observed in male rats dosed by gavage to 175 mg/kg/day (plasma AUC for HMG-CoA reductase inhibitory activity 14 times higher than in humans dosed at 80 mg/day) and male fertility was not affected in either study. No adverse effects on fertility or reproduction were observed in female rats given doses up to 225 mg/kg/day (plasma AUC for enzyme inhibitory activity 56 times higher than in humans dosed at 80 mg/day). Atorvastatin caused no adverse effects on sperm or semen parameters, or on reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years (Plasma AUC for enzyme inhibitory activity 13 times higher than in humans).

Use in Pregnancy

Pregnancy Category D

The definition of Pregnancy Category D is 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.

ATOZET 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).

ATOZET 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 in combination with statins, including atorvastatin, 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.

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.

Atorvastatin

Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women.

HMG-CoA reductase inhibitors are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

Atorvastatin crosses the rat placenta and reaches a level in foetal liver equivalent to that in maternal plasma. Animal reproduction studies showed no evidence of teratogenic activity in rats or rabbits at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. Increased post-implantation loss, decreased foetal weight and increased skeletal variations were observed in rats dosed at 100–300 mg/kg/day and rabbits dosed at 50–100 mg/kg/day. In a peri/post natal study, rats dosed at 225 mg/kg/day showed an increased incidence of stillbirths, decreases in birthweight, an increased incidence of dilated renal pelvis, increased postnatal mortality, suppression of pup growth, retardation of physical development and abnormal behavioural development; some of these effects were also observed at the non-maternotoxic dose of 100 mg/kg/day; the plasma AUC for HMG-CoA reductase inhibitory activity at the no effect dose level of 20 mg/kg/day was similar to that in humans dosed at 80 mg/day.

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 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 atorvastatin.

Studies in rats have shown that ezetimibe and atorvastatin are excreted in milk. It is not known whether ezetimibe or atorvastatin are excreted into human breast milk, therefore, women who are breast feeding should not take ATOZET (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.

In rats, plasma concentrations of atorvastatin are similar to those in milk.

Paediatric Use

There are insufficient data for the safe and effective administration of ATOZET in paediatric patients.

Use in the Elderly

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

Co-administration of ezetimibe and atorvastatin was studied in 1053 patients ≥ 65 years of age with hypercholesterolaemia and high risk for CHD. Patients received ezetimibe 10 mg and atorvastatin doses from 10 to 40 mg daily. The treatments were well tolerated, with a similar safety profile to that observed in younger patients.

Atorvastatin

Treatment experience in adults aged ≥70 years with doses of atorvastatin up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of atorvastatin in this population were similar to those of patients <70 years of age.

Genotoxicity

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.

Atorvastatin

Atorvastatin did not demonstrate mutagenic or clastogenic potential in an appropriate battery of assays. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

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 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.

Atorvastatin

In a 2-year study in rats given 10, 30 or 100 mg/kg/day, the incidence of hepatocellular adenoma was marginally, although not significantly, increased in females at 100 mg/kg/day. The maximum dose used was 11 times higher than the highest human dose (80 mg/kg) based on AUC (0–24) values. In a 2-year study in mice given 100, 200, or 400 mg/kg, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. The maximum dose used was 14 times higher than the highest human dose (80 mg/kg) based on AUC (0-24) values. Other HMG-CoA reductase inhibitors have been reported to induce hepatocellular tumours in mice and rats.

Effect on Ubiquinone Levels (COQ_{10})

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term, statin-induced deficiency of ubiquinone has not been established.

Effect on Lipoprotein (a)

Like other HMG-CoA reductase inhibitors, atorvastatin has variable effects on lipoprotein (a) (Lp (a)). It is unclear whether the beneficial effects of lowering LDL-C and total cholesterol in some patients may be blunted by raised Lp (a) levels.

Effect on Laboratory Tests

ATOZET can cause elevations in ALT/AST, alkaline phosphatase, GGT, bilirubin and creatine kinase.

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 ATOZET may affect some patients' ability to drive or operate machinery. Individual responses to ATOZET may vary (see ADVERSE EFFECTS).

INTERACTIONS WITH OTHER MEDICINES

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with atorvastatin.

Cytochrome P450

Inhibitors of 3A4

Atorvastatin

Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and

potentiation of effects depends on the variability of effect on cytochrome P450 3A4. Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have been noted with HIV protease inhibitors (fosamprenavir and combinations of lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenivir/ritonavir), hepatitis C protease inhibitors (boceprevir), clarithromycin and itraconazole. In patients taking cyclosporin, the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of ATOZET should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing ATOZET and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir or fosamprenivir plus ritonavir, or the hepatitis C protease inhibitor boceprevir, the dose of ATOZET should not exceed 10/20 mg and should be used with caution (see PRECAUTIONS, Skeletal Muscle and DOSAGE and ADMINISTRATION, Cyclosporin, Clarithromycin, Itraconazole or Certain Protease Inhibitors). In patients taking the HIV protease inhibitor nelfinavir, the dose of ATOZET should not exceed 10/40 mg and close clinical monitoring is recommended. Based on experience with other HMG-CoA reductase inhibitors caution should be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. macrolide antibiotics including erythromycin and clarithromycin, and azole antifungals including itraconazole). The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, azole antifungals or niacin:

Erythromycin/Clarithromycin: In healthy individuals, co-administration of atorvastatin (10mg QD) and erythromycin (500mg QID), or clarithromycin (500mg BID), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin. In patients taking clarithromycin the dose of ATOZET should not exceed 10/20 mg (see PRECAUTIONS, Skeletal Muscle).

Protease Inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Itraconazole: Concomitant administration of atorvastatin (20 to 40mg) and itraconazole (200mg) was associated with an increase in atorvastatin AUC. In patients taking itraconazole the dose of ATOZET should not exceed 10/20 mg.

Diltiazem Hydrochloride: Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Grapefruit Juice: Contains one or more components that inhibit cytochrome P450 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L per day).

Ezetimibe

Cimetidine: Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Inducers of 3A4

Atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4.

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin, phenytoin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter (OATP1B1), simultaneous co-administration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.

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.

Other Drug Interactions

Ezetimibe

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyloestradiol and levonorgestrel), glipizide, tolbutamide or midazolam during co-administration.

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.

Atorvastatin

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with atorvastatin decreased atorvastatin plasma concentrations approximately 35%, however, LDL-C reduction was not altered.

Bile Acid Sequestrants

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

Colestipol

Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

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.

Fibrates

The safety and effectiveness of ezetimibe and atorvastatin administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of ezetimibe and atorvastatin with fibrates is not recommended until use in patients is studied.

Fenofibrate

Caution should be used when prescribing ATOZET and fenofibrate, as fenofibrate can cause myopathy when given alone.

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

Gemfibrozil

Concomitant administration of ATOZET with gemfibrozil should be avoided.

In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. No clinical data are available.

Anticoagulants

The effect of ATOZET on the prothrombin time has not been studied.

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 or fluindione. Most of these patients were also on other medications (see PRECAUTIONS).

Atorvastatin

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration 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.

Although interaction studies with atorvastatin and fusidic acid have not been conducted, there have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, ATOZET treatment should be

discontinued throughout the duration of the fusidic acid treatment (see CONTRAINDICATIONS and PRECAUTIONS, Skeletal Muscle).

Colchicine

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing ATOZET with colchicine (see PRECAUTIONS).

Transporter Inhibitors

Atorvastatin

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10mg and cyclosporin 5.2mg/kg/day resulted in an increase in exposure to atorvastatin. The co-administration of ATOZET with cyclosporin should be avoided (see PRECAUTIONS, Skeletal Muscle and DOSAGE AND ADMINISTRATION).

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).

Digoxin

When multiple doses of digoxin (0.25mg QD) and 10mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, steady-state plasma digoxin concentrations increased by approximately 20% following administration of digoxin with 80mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives

Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyloestradiol increased AUC values for norethindrone and ethinyl oestradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking ATOZET.

Other Medicines shown not to interact with atorvastatin

Amlodipine

Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80mg daily and amlodipine 10mg daily at steady-state. In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80mg and amlodipine 10mg resulted in an 18% increase in exposure to atorvastatin, which was not clinically meaningful.

Azithromycin

Co-administration of atorvastatin 10mg daily and azithromycin (500mg QD) did not alter the plasma concentrations of atorvastatin.

Other concomitant therapy

In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with all specific agents have not been conducted.

ADVERSE EFFECTS

Co-administration of ezetimibe and atorvastatin has been evaluated for safety in more than 2,400 patients in 7 clinical trials. Co-administration of ezetimibe and atorvastatin was generally well-tolerated. Table 7 summarises the common (≥ 1.0% in any group) drug-related adverse events by system organ class and preferred term.

Table 7
Drug-related Adverse Events Occurring in ≥1.0% in Patients Receiving Atorvastatin or Co-Administered Ezetimibe and Atorvastatin[a]

	Atorvastatin[a] (%) N=2521	Co-administered ezetimibe and atorvastatin[a] (%) N=2523
Gastrointestinal disorders		
Diarrhoea	0.7	1.0
Musculoskeletal and connective tissue disorders		
Myalgia	1.2	1.5

[a] All doses

In a placebo-controlled clinical trial in 628 patients with hyperlipidaemia (P0692), in which patients were treated for up to 12 weeks, the most commonly reported adverse reactions (incidence ≥2% and greater than placebo) were:

Table 8

Clinical and Selected Laboratory Adverse Reactions Occurring in ≥ 2% of Patients Treated with Co-Administered Ezetimibe and Atorvastatin* and at an Incidence Greater then Placebo, Regardless of Causality

Body System / Organ Class Adverse Reaction	Placebo (%) N=60	Ezetimibe 10 mg (%) N=65	Atorvastatin† (%) N=248	Eze/Atorva† (%) N=255
Nervous system disorders				
Dizziness	0	6	<1	2
Respiratory, thoracic, and mediastinal disorders				
Coughing	0	3	<1	2
Gastrointestinal disorders				
Abdominal pain	2	2	4	3
Nausea	0	2	5	3
Musculoskeletal and connective tissue disorders				
Arthralgia	0	5	6	3
Muscle weakness	0	2	0	2
Musculoskeletal pain	3	8	5	4
Metabolism and nutrition disorders				
Hyperkalaemia	0	0	<1	2
Infections and infestations				
Bronchitis	0	2	2	2
Sinusitis	0	3	2	2
Vascular disorders				
Hot flushes	0	0	<1	2
Investigations				
ALT increased	0	0	2	5
AST increased	0	0	<1	4

* Equivalent to ATOZET

† All doses

The following other uncommon (≥1/1000, <1/100) drug-related adverse experiences by system organ class and preferred term were reported in patients taking co-administered ezetimibe and atorvastatin:

Infections and Infestations: Uncommon: influenza

Psychiatric disorders: Uncommon: depression, insomnia, sleep disorder

Nervous system disorders: Uncommon: dysgeusia, paraesthesia, dizziness, headache

Respiratory, thoracic and mediastinal disorders: dyspnoea

Cardiac disorders: Uncommon: sinus bradycardia

Vascular disorders: Uncommon: hot flush

Gastrointestinal disorders: Uncommon: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, frequent bowel movements, stomach discomfort, upset stomach, abdominal distension, constipation, dyspepsia, flatulence, gastritis, nausea

Skin and subcutaneous tissue disorders: Uncommon: acne; urticaria

Musculoskeletal and connective tissue disorders: Uncommon: arthralgia, back pain, muscle fatigue, muscular weakness, pain in extremity, muscle spasms, musculoskeletal stiffness

General disorders and administration site conditions: Uncommon: asthenia, oedema, fatigue, malaise

Investigations: Uncommon: ALT and/or AST increased, alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, weight increased, blood CK increased.

Laboratory Values

In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ³ 3 X ULN, consecutive) was 0.6% for patients treated with co-administered ezetimibe and atorvastatin. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy (See PRECAUTIONS).

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2, 0.2, 0.6, and 2.3% for 10, 20, 40, and 80mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

In controlled clinical studies, the incidence of consecutive elevations (³ 3 X the upper limit of normal [ULN]) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

Discontinuations

Gastrointestinal disorders and musculoskeletal and connective tissue disorders contributed to the majority of adverse experiences which lead to discontinuation in clinical trials. A total of 37 (0.7%) of 5169 patients discontinued due to gastrointestinal adverse experiences; 2 (3.3%) of 60 patients in the placebo group, 0 of 65 patients in the ezetimibe monotherapy group, 20

(0.8%) of 2521 patients in the atorvastatin monotherapy group, and 15 (0.6%) of 2523 patients in the ezetimibe + atorvastatin coadministration group. A total of 28 (0.5%) of 5169 patients discontinued due to musculoskeletal adverse experiences; 13 (0.5%) of 2521 patients on atorvastatin monotherapy and 15 (0.6%) of 2523 patients on ezetimibe + atorvastatin. The most frequently reported adverse experiences causing discontinuation were nausea; 7 (0.3%) and 3 (0.1%) patients, respectively, and myalgia, 8 (0.3%) and 8 (0.3%) patients, respectively, in the atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups.

In a ATOZET (ezetimibe and atorvastatin) placebo-controlled clinical trial, 628 patients (age range 18-86 years, 59% women, 85% Caucasians, 6% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 12 weeks, 6% of patients on ATOZET and 5% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with ATOZET that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Myalgia (0.8%)
- Abdominal pain (0.8%)
- Increased hepatic enzymes (0.8%)

Post-marketing Experience and Other Clinical Trial Experience

The following additional adverse reactions have been reported in post-marketing use with co-administered ezetimibe and atorvastatin or in clinical studies or post-marketing use with ezetimibe or atorvastatin. Not all effects listed have been causally associated with ezetimibe or atorvastatin.

Eye disorders: vision blurred

Infections and infestations: nasopharyngitis, urinary tract infection, infection, sinusitis, pharyngitis

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Metabolism and nutrition disorders: decreased appetite, anorexia, hyperglycaemia; hypoglycaemia

Nervous system disorders: hypoesthesia, dysgeusia, amnesia, peripheral neuropathy

Psychiatric disorders: nightmare

Ear and labyrinth disorders: tinnitus, deafness

Vascular disorders: hypertension, haemorrhagic stroke

Respiratory, thoracic, and mediastinal disorders: cough, pharyngolaryngeal pain, epistaxis, asthma

Gastrointestinal disorders: pancreatitis, gastroesophageal reflux disease, eructation, vomiting, dry mouth

Hepatobiliary disorders: hepatitis, cholelithiasis, cholecystitis, hepatic failure, cholestasis

Skin and subcutaneous tissue disorders: pruritus, skin rash, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis), alopecia

Musculoskeletal and connective tissue disorders: immune mediated necrotising myopathy, myopathy/rhabdomyolysis which may be fatal (examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure and cardiac arrhythmia (See PRECAUTIONS), neck pain, joint swelling, musculoskeletal pain, myositis

Reproductive system and breast disorders: gynaecomastia, erectile dysfunction

General disorders and administration site conditions: chest pain, pain, oedema peripheral, pyrexia

Injury, poisoning and procedural complications: tendon rupture, injury

Investigations: white blood cells urine positive

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see PRECAUTIONS)
- Diabetes mellitus: frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension)

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed an increased risk of haemorrhagic stroke in patients with prior haemorrhagic stroke or prior lacunar infarct (see PRECAUTIONS).

In ASCOT (see CLINICAL TRIALS, Prevention of Cardiovascular Disease) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

There has been rare postmarketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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 (PY) 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.

Please see the individual Product Information documents for atorvastatin and ezetimibe for further information on adverse effects.

DOSAGE AND ADMINISTRATION

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

Patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ATOZET.

ATOZET can be administered within the dosage range of 10/10 mg to 10/80 mg as a single daily dose. The recommended starting dose of ATOZET 10/10 mg or 10/20 mg once daily. ATOZET can be administered at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy, and the patient's response. After initiation and/or upon titration of ATOZET, lipid levels should be re-analysed within 2 or more weeks and dosage adjusted according to the patient's response.

Advice to Patients Currently Taking Ezetimibe and/or Atorvastatin

To prevent accidental excessive dosing due to inadvertent duplication of administration of ezetimibe and/or atorvastatin, patients currently taking ezetimibe and/or atorvastatin should be advised that ATOZET replaces these medications and therefore the current ezetimibe and/or atorvastatin medication(s) should no longer be taken. Patients should also be advised to take any remaining medication(s) to the pharmacy for appropriate disposal.

Dosage in Patients with Homozygous Familial Hypercholesterolaemia (HoFH)

The dosage of ATOZET in patients with homozygous familial hypercholesterolemia is 10/40 mg or 10/80 mg daily. ATOZET should be used as an adjunct to other treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Renal Insufficiency

No dosage adjustment is required for renally impaired patients.

Hepatic insufficiency

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh A or score 5 to 6). Treatment with ATOZET is not recommended in patients with moderate (Child Pugh B or score 7 to 9) or severe (Child Pugh C or score > 9) liver dysfunction. The benefits of therapy should be weighed against the risks when ATOZET is to be given to patients with hepatic insufficiency (see PHARMACOLOGY; CONTRAINDICATIONS, and PRECAUTIONS)

Use in Combination with Other Medicinal Compounds

Bile Acid Sequestrants

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

Cyclosporin, Clarithromycin, Itraconazoleor Certain Protease Inhibitors

In patients taking cyclosporin or the HIV protease inhibitors tipranavir plus ritonavir or the hepatitis C protease inhibitor telaprevir, therapy with ATOZET should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing ATOZET and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or the hepatitis C protease inhibitor boceprevir, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with ATOZET should be limited to 10/20 mg, and appropriate clinical

assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir, therapy with ATOZET should be limited to 10/40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of ATOZET is employed (see PRECAUTIONS, Skeletal muscle and INTERACTIONS WITH OTHER MEDICINES).

Use in the Elderly

No dosage adjustment is required for elderly patients for ATOZET (See PHARMACOLOGY, Characteristics in Patients, (Special Populations).

Paediatric Use

Treatment with ATOZET is not recommended.

OVERDOSAGE

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of an overdose.

No specific treatment of overdosage with ATOZET 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, 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Atorvastatin

If there has been significant ingestion, consider administration of activated charcoal. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. For rhabdomyolysis, administer sufficient 0.9% saline to maintain urine output of 2 to 3mL/kg/hr. Diuretics may be necessary to maintain urine output. Urinary alkalinisation is not routinely recommended. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

PRESENTATION AND STORAGE CONDITIONS

ATOZET 10/10 contains 10 mg of ezetimibe and 10.9 mg of atorvastatin calcium trihydrate, equivalent to 10 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 257 on one side and plain on the other.

ATOZET 10/20 contains 10 mg of ezetimibe and 21.7 mg of atorvastatin calcium trihydrate, equivalent to 20 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 333 on one side and plain on the other.

ATOZET 10/40 contains 10 mg of ezetimibe and 43.4 mg of atorvastatin calcium trihydrate, equivalent to 40 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 337 on one side and plain on the other.

ATOZET 10/80 contains 10 mg of ezetimibe and 86.8 mg of atorvastatin calcium trihydrate, equivalent to 80 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 357 on one side and plain on the other.

Available as 10 (starter) and 30 tablet blister (aluminium/aluminium) packs.

Store below 30°C and in a dry place.

NAME AND ADDRESS OF THE 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 ARTG

4th February 2015

DATE OF MOST RECENT AMENDMENT

21st January 2015

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PRODUCT INFORMATION

ZETEZE®

[ezetimibe, atorvastatin (as calcium trihydrate)]

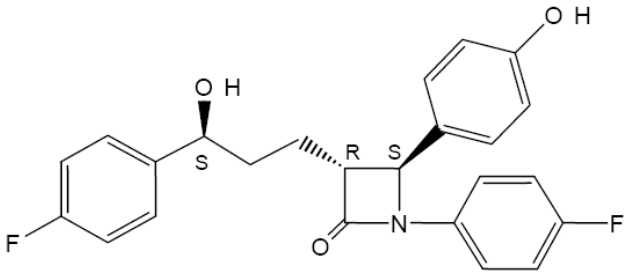
ZETEZE 10 mg/10 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 10 mg
ZETEZE 10 mg/20 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 20 mg
ZETEZE 10 mg/40 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 40 mg
ZETEZE 10 mg/80 mg containing ezetimibe 10 mg and atorvastatin (as calcium trihydrate) 80 mg

NAME OF THE MEDICINE

ZETEZE is a film-coated tablet containing ezetimibe 10mg and atorvastatin 10, 20, 40 or 80 mg.

Ezetimibe

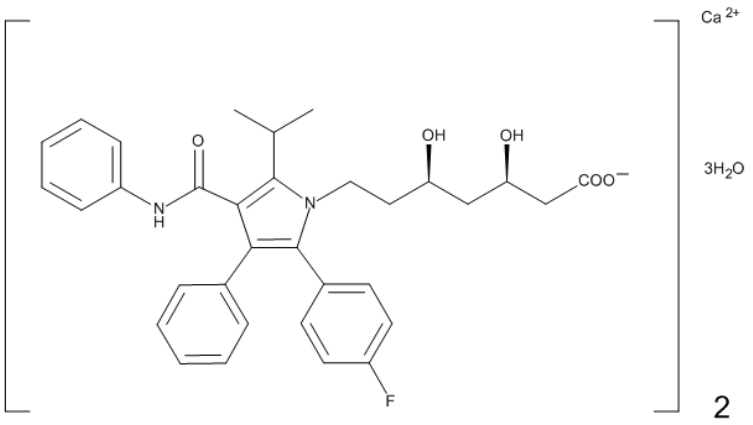
The chemical name of ezetimibe is 1-(4-fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone. The CAS registry number is 163222-33-1. The empirical formula is $C_{24}H_{21}F_2NO_3$. Its molecular weight is 409.4 and its structural formula is:



Atorvastatin

Atorvastatin is [*R*-(*R**,*R**)]-2-(4-fluorophenyl)-b, d-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl] -1*H*-pyrrole -1-heptanoic acid, calcium salt (2:1) trihydrate.

The CAS registry number is 344423-98-9. The molecular formula of atorvastatin calcium trihydrate is $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$. The molecular weight of atorvastatin calcium trihydrate 1209.36. Its structural formula is:



DESCRIPTION

ZETEZE is available for oral use as tablets containing 10 mg of ezetimibe and: 10.9 mg of atorvastatin calcium trihydrate, equivalent to 10 mg of atorvastatin (ZETEZE 10 mg/10 mg); 21.7 mg of atorvastatin calcium trihydrate, equivalent to 20 mg of atorvastatin (ZETEZE 10 mg/20 mg); 43.4 mg of atorvastatin calcium trihydrate, equivalent to 40 mg of atorvastatin (ZETEZE 10 mg/40 mg); or 86.8 mg of atorvastatin calcium trihydrate, equivalent to 80 mg of atorvastatin (ZETEZE 10 mg/80 mg).

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.

Atorvastatin calcium trihydrate is a white or almost-white powder that is soluble in dimethyl sulfoxide. The degree of solubility in water, ethanol and methylene chloride is very slightly soluble to practically insoluble.

Each film-coated tablet of ZETEZE contains the following inactive ingredients: calcium carbonate, silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone and sodium lauryl sulfate.

The film coating contains: hypromellose, macrogol 8000, titanium dioxide and purified talc.

PHARMACOLOGY

Mechanism of action

ZETEZE (ezetimibe/atorvastatin) is a lipid-lowering product that selectively inhibits the intestinal absorption of cholesterol and related plant sterols and inhibits the endogenous synthesis of cholesterol.

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. ZETEZE contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. Together these distinct mechanisms reduce total-C, LDL-C, Apo B, TG, and non-HDL-C, and increase HDL-C beyond either treatment alone, through dual inhibition of cholesterol absorption and synthesis.

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.

Ezetimibe

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. 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, ethinyloestradiol, or the fat soluble vitamins A and D.

Atorvastatin

Atorvastatin is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides (TG) and cholesterol in the liver are incorporated into very low density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. Low density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a marked and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Atorvastatin reduces total-C, LDL-C, and Apo B in both normal volunteers and in patients with homozygous and heterozygous familial hypercholesterolaemia (FH), non-familial forms of hypercholesterolaemia, and mixed dyslipidaemia. Atorvastatin also reduces very low density lipoprotein cholesterol (VLDL-C) and TG and produces variable increases in HDL-C and apolipoprotein A-1. Atorvastatin reduces total-C, LDL-C, VLDL-C, Apo B and TG, and increases HDL-C in patients with isolated hypertriglyceridaemia. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinaemia. In animal models, atorvastatin limits the development of lipid-enriched atherosclerotic lesions and promotes the regression of pre-established atheroma.

Atorvastatin and its metabolites are responsible for pharmacological activity in humans. The liver is its primary site of action and the principal site of cholesterol synthesis and LDL clearance. Drug dose rather than systemic drug concentration correlates better with LDL-C reduction. Individualisation of drug dose should be based on therapeutic response (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics

ZETEZE has been shown to be bioequivalent at the high and low end of dosage to coadministration of corresponding doses of ezetimibe and atorvastatin tablets. Bioequivalence at the mid dose ranges has been extrapolated.

The effects of a high-fat meal on the pharmacokinetics of ezetimibe and atorvastatin when administered as ZETEZE tablets are comparable to those reported for the individual tablets.

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 ezetimibe 10 mg tablets.

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.

Atorvastatin

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. A constant proportion of atorvastatin is absorbed intact. The absolute bioavailability is 14%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration (see DOSAGE AND ADMINISTRATION).

Distribution

The mean volume of distribution of atorvastatin is about 400 litres. Atorvastatin is ≥98% bound to plasma proteins. A RBC/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin is likely to be secreted in human milk (see PRECAUTIONS).

Metabolism

In humans, atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives. In vitro inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. In vitro studies suggest the importance of atorvastatin metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme (see PRECAUTIONS). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Characteristics in Patients (Special Populations)

Paediatric Patients

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.

Atorvastatin

Pharmacokinetic studies have not been conducted in the paediatric population.

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.

Atorvastatin

Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Lipid effects are comparable to that seen in younger patient populations given equal doses of atorvastatin.

Gender

Ezetimibe

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

Atorvastatin

Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men; however, there is no clinically significant difference in lipid effects with atorvastatin between men and women.

Race

There are no pharmacokinetic data on the co-administration of ezetimibe and atorvastatin in non-Caucasians.

Ezetimibe

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

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).

Atorvastatin

Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (see CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 to be 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.

Atorvastatin

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see DOSAGE AND ADMINISTRATION).

Haemodialysis

Haemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Despite the expected cholesterol changes, no cardiovascular benefit with atorvastatin has been demonstrated in haemodialysis patients. ZETEZE has not been studied in this population.

CLINICAL TRIALS

In controlled clinical studies, ZETEZE (co-administration of ezetimibe and atorvastatin) significantly reduced total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increased high-density lipoprotein cholesterol (HDL-C) in patients with hypercholesterolaemia.

No incremental benefit of ZETEZE on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

Primary Hypercholesterolaemia

ZETEZE

Ezetimibe Initiated Concurrently with Atorvastatin

In a multicentre, double-blind, placebo-controlled, clinical study (P0692) in patients with hyperlipidaemia, 628 patients (260 male, 368 female) were treated for up to 12 weeks and 246 for up to an additional 48 weeks. Patients were 18 to 86 years of age, with baseline LDL-C concentrations between 130 to 253 mg/dL (3.37 to 6.55 mmol/L) (mean baseline LDL-C ranged from 175 and 184 mg/dL [4.53 and 4.77 mmol/L] across treatment groups). Sixty-three percent had risk factors or a history of cardiovascular disease. Patients were randomised

to receive placebo, ezetimibe (10 mg), atorvastatin (10 mg, 20 mg, 40 mg, or 80 mg), or co-administered ezetimibe and atorvastatin equivalent to ZETEZE (10/10, 10/20, 10/40, and 10/80) in the 12-week study. After completing the 12-week study, eligible patients were assigned to co-administered ezetimibe and atorvastatin equivalent to ZETEZE (10/10-10/80) or atorvastatin (10-80 mg/day) for an additional 48 weeks (See CLINICAL TRIALS, *Long term studies*, P2154).

Eight percent of subjects discontinued treatment early, 5% were due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation.

Patients receiving all doses of ZETEZE were compared to those receiving all doses of atorvastatin. The primary endpoint was percent change from baseline in direct LDL-C at study endpoint (12 weeks). Secondary endpoints were percent change from baseline in calculated LDL-C, TC, TG, HDL-C and Apo B at endpoint. ZETEZE lowered total C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone. (See Table 1)

Table 1
Response to ZETEZE in Patients with Primary Hyperlipidaemia (ITT analysis)
(Mean[a] % change from Untreated Baseline[b] at 12 weeks)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG[a]	HDL-C	Non-HDL-C
Pooled data (All ZETEZE doses)[c]	255	-41	-56	-45	-33	+7	-52
Pooled data (All atorvastatin doses)[c]	248	-32	-44	-36	-24	+4	-41
Ezetimibe 10 mg	65	-14	-20	-15	-5	+4	-18
Placebo	60	+4	+4	+3	-6	+4	+4
ZETEZE by dose							
10/10	65	-38	-53	-43	-31	+9	-49
10/20	62	-39	-54	-44	-30	+9	-50
10/40	65	-42	-56	-45	-34	+5	-52
10/80	63	-46	-61	-50	-40	+7	-58
Atorvastatin by dose							
10 mg	60	-26	-37	-28	-21	+6	-34
20 mg	60	-30	-42	-34	-23	+4	-39
40 mg	66	-32	-45	-37	-24	+4	-41
80 mg	62	-40	-54	-46	-31	+3	-51

a For triglycerides, median % change from baseline
b Baseline – on no lipid-lowering drug
c ZETEZE pooled (10/10-10/80) significantly reduced total-C, LDL-C, Apo B, TG, non-HDL-C, and significantly increased HDL-C compared to all doses of atorvastatin pooled (10-80 mg).

The changes in lipid endpoints after an additional 48 weeks of treatment with ZETEZE (all doses) or with atorvastatin (all doses) were generally consistent with the 12-week data displayed above.

Ezetimibe Added to Stable Atorvastatin Therapy

In a multicentre, double-blind, placebo-controlled, 8-week study (P2173/2246), 769 (443 male, 326 female) patients aged 22 to 85 years with hypercholesterolaemia (baseline LDL-C ranged from 71 to 455 mg/dL [1.84 to 11.78 mmol/L]; mean baseline LDL-C 138 to 139 mg/dL [3.57 to 3.60 mmol/L] across the treatment groups), 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 ezetimibe 10 mg or placebo in addition to their on-going statin therapy. Sixty-eight percent of subjects had CHD, diabetes and/or CHD equivalent disease with LDL-C ≥ 100 mg/dL (≥2.59 mmol/L).

Fifty-three subjects discontinued study treatment early, 34 were due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or the reasons for discontinuation.

The primary efficacy endpoint was the difference in mean percent change in LDL-C between the treatment groups. The secondary endpoints included the percentage of subjects who achieved NCEP ATP II target LDL-C levels. Endpoints were analysed for a modified ITT population (all subjects who received randomised treatment and had at least one post-baseline value).

Three percent of subjects discontinued treatment early due to adverse events in each treatment group.

In the subgroup of 308 patients with hypercholesterolaemia already receiving atorvastatin monotherapy and not at LDL-C goal at baseline (~83%), significantly more patients randomised to ezetimibe co-administered with atorvastatin achieved their LDL-C goal at study endpoint compared to patients randomised to placebo co-administered with atorvastatin, 72% vs. 27%; the analysis was post-hoc. Ezetimibe added to atorvastatin therapy lowered LDL-C significantly more than placebo added to atorvastatin therapy, 25% vs. 4%. In addition, ezetimibe added to atorvastatin therapy significantly decreased total-C, Apo B, and TG compared with placebo added to atorvastatin therapy.

After 8 weeks of treatment, 730 patients had their blinded ezetimibe or placebo withdrawn and were continued on their stable statin therapy for another 6 weeks (P2173R). Twenty-one subjects discontinued treatment during the reversibility phase. Lipid parameters were observed to return to their pre-treatment values during this period, without any evidence of rebound.

Another double-blind, randomised, placebo-controlled study (P040) evaluated the effect of ezetimibe 10 mg/day added to ongoing statin therapy vs. continued statin therapy alone (at unchanged dose) in 3030 patients (52% male) mean age 62 years and with hypercholesterolemia who were not at their NCEP ATP III Target LDL-C level. Mean baseline LDL-C was 129 mg/dL (3.34 mmol/L). Approximately 78% of patients had CHD or risk equivalent. Adverse experiences resulting in discontinuation occurred in 2.1% of the statin monotherapy groups and in 1.4% of the ezetimibe/statin groups.

The primary outcome was percent change in LDL-C from baseline at week 6. In the subgroup of patients receiving atorvastatin (n=1194) the addition of ezetimibe to atorvastatin produced a reduction of 27.2% in LDL-C at week 6 (relative to the on-statin baseline) compared to 4.2% for placebo, a difference of 23.0% (Modified ITT analysis – excluded patients who had adverse clinical or laboratory experiences, lost to follow-up,

protocol deviations, withdrawn consent, discontinued for other reasons and missing LDL-C measurements).In addition, a greater number of patients in the active ezetimibe group achieved their NCEP ATP III Target Goal for LDL-C, 23.9% for atorvastatin alone vs. 74.6% for ezetimibe + atorvastatin (secondary outcome).

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

A multicentre, double-blind, controlled, 14-week study (P00693) was conducted in 621 patients (330 male, 291 female) with heterozygous familial hypercholesterolemia (HeFH), coronary heart disease (CHD), or multiple cardiovascular risk factors (≥2), adhering to an National Cholesterol Education Program (NCEP) Step I or stricter diet. Patients were 18 to 82 years of age with baseline LDL-C of 117 to 466 mg/dL (3.03 to 12.07 mmol/L) (mean LDL-C : 186 mg/dL and 187 mg/dL [4.82 mmol/L and 4.84 mmol/L] for patients receiving co-administered ezetimibe and atorvastatin 10/10 and atorvastatin 20 mg respectively). Fifty-eight percent of patients were diagnosed with HeFH and the majority of subjects (87%) had risk factors or a family history of cardiovascular disease.

All patients received atorvastatin 10 mg for a minimum of 4 weeks prior to randomisation. Patients were then randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ZETEZE 10/10) or atorvastatin 20 mg/day monotherapy. Patients who did not achieve their LDL-C target goal after 4 and/or 9 weeks of randomised treatment were titrated to double the atorvastatin dose. There were 181 patients in the atorvastatin monotherapy treatment arm (all doses) and 181 in the co-administration arm (all doses).

Nine percent of subjects discontinued treatment early, 4% due to adverse events. There was no trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation.

Efficacy analyses were carried out on an ITT basis.

The primary endpoint was proportion of subjects achieving target LDL-C levels of ≤ 2.59 mmol/L (≤ 100 mg/dL) at week 14. A higher proportion of subjects on ZETEZE (22%), than on atorvastatin alone (7%) achieved target LDL-C levels of ≤ 2.59 mmol/L (100 mg/dL) at week 14 ($p<0.01$).

The secondary endpoints included mean percent change from baseline in LDL-C and proportion of subjects achieving target LDL-C levels at week 4. ZETEZE 10/10 was significantly more effective than doubling the dose of atorvastatin to 20 mg in further reducing total-C, LDL-C, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (See Table 2.) In addition, at week 4 significantly more patients receiving ZETEZE 10/10 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 20 mg, 12% vs. 2%. The baseline mean LDL-C levels for patients receiving ZETEZE 10/10 and atorvastatin 20 mg were 186 mg/dL and 187 mg/dL, respectively.

Table 2
Response to ZETEZE after 4 Weeks in Patients with CHD or Multiple Cardiovascular Risk Factors and an LDL-C ≥130 mg/dL (≥3.37 mmol/L) (Modified ITT analysis)
(Mean* % Change from Baseline†)

Treatment (Daily Dose)	N	Total-C	LDL-C	HDL-C	TG*	Non-HDL-C
ZETEZE 10/10	305	-17‡	-24‡	+2	-9‡	-22‡
Atorvastatin 20 mg	316	-6	-9	+1	-4	-8

*For triglycerides, median % change from baseline
†Patients on atorvastatin 10 mg, then switched to ZETEZE 10/10 or titrated to atorvastatin 20 mg
‡p<0.05 for difference with atorvastatin

The Titration of Atorvastatin Versus Ezetimibe Add-On to Atorvastatin in Patients with Hypercholesterolaemia (TEMPO) study, a multicentre, double-blind, controlled, 6-week study (P079), included 184 patients (55% male) mean age 57 (range 24 to 78 years) with an LDL-C level ≥2.6 mmol/L and ≤4.1 mmol/L (≥100 mg/dL and ≤160 mg/dL), mean baseline LDL-C of 3.08 mmol/L (118.9 mg/dL) and at moderate high risk for coronary heart disease (CHD). All patients received atorvastatin 20 mg for a minimum of 4 weeks prior to randomisation. Patients not at the optional NCEP ATP III LDL-C level (<2.6 mmol/L [<100 mg/dL]) were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ZETEZE 10/20) or atorvastatin 40 mg for 6 weeks. Thirteen patients discontinued study treatment; 2 were due to adverse events.

The primary endpoint was percent change from baseline LDL-C at week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). ZETEZE 10/20 was significantly more effective than doubling the dose of atorvastatin to 40 mg in further reducing total-C, LDL-C, Apo B and non-HDL-C. Results for HDL-C and TG between the two treatment groups were not significantly different (See Table 3). In addition, significantly more patients receiving ZETEZE 10/20 attained LDL-C <2.6 mmol/L (<100 mg/dL) compared to those receiving atorvastatin 40 mg, 84% vs. 49% (secondary endpoint).

Table 3
Response to ZETEZE in Patients with Primary Hypercholesterolaemia (Modified ITT analysis)
(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ZETEZE 10/20	92	-20[c]	-31[c]	-21[c]	+3	-18	-27[c]
Atorvastatin 40 mg	92	-7	-11	-8	+1	-6	-10

a For triglycerides, median % change from baseline
b Patients on atorvastatin 20 mg, then switched to ZETEZE 10/20 or titrated to atorvastatin 40 mg
c $p<0.05$ for difference with atorvastatin

The Ezetimibe Plus Atorvastatin Versus Atorvastatin Titration in Achieving Lower LDL-C Targets in Hypercholesterolemic Patients (EZ-PATH) study, a multicentre, double-blind, controlled, 6-week study (P090), included 556 (60% male) patients with a mean age of 61 years and an LDL-C level ≥1.8 mmol/L and ≤4.1 mmol/L (≥70 mg/dL and ≤160 mg/dL) and at high risk for coronary heart disease (CHD). All patients received atorvastatin 40 mg for a minimum of 4 weeks prior to randomisation. Patients not at the optional NCEP ATP III LDL-C level <1.8 mmol/L (<70 mg/dL) were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ZETEZE 10/40) or atorvastatin 80 mg for 6 weeks. Four patients in the ezetimibe/atorvastatin group and 6 patients in the atorvastatin monotherapy group experienced an adverse event that lead to discontinuation of the study treatment.

The primary outcome was mean percent change from baseline in LDL-C at week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). ZETEZE 10/40 was significantly more effective than doubling the dose of atorvastatin to 80 mg in further reducing total-C, LDL-C, Apo B, TG, and non-HDL-C. Results for HDL-C between the two treatment groups were not significantly different (See Table 4). In addition, significantly more patients receiving ZETEZE 10/40 attained LDL-C <1.8 mmol/L (<70 mg/dL) compared to those receiving atorvastatin 80 mg, 74% vs. 32% (secondary endpoint).

Table 4
Response to ZETEZE in Patients with Primary Hypercholesterolaemia (Modified ITT analysis)
(Mean[a] % Change from Baseline[b])

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	HDL-C	TG[a]	Non-HDL-C
ZETEZE 10/40	277	-17[c]	-27[c]	-18[c]	0	-12[c]	-23[c]
Atorvastatin 80 mg	279	-7	-11	-8	-1	-6	-9

a For triglycerides, median % change from baseline
b Patients on atorvastatin 40 mg, then switched to ZETEZE 10/40 or titrated to atorvastatin 80 mg
c $p<0.05$ for difference with atorvastatin

A multicentre, randomised, double-blind, parallel arm, 12-week study (P112) evaluated the lipid altering efficacy and safety of the addition of ezetimibe 10 mg to atorvastatin 10 mg, as compared to doubling the dose of atorvastatin from 10 mg to 20 mg and followed by further up-titration from atorvastatin 20 to 40 mg. The 1053 patients (53.3% female) were 65 years

of age and older (mean age 71.2; range 65 to > 90 years), at high risk for CHD with or without diagnosed atherosclerotic vascular disease (AVD) who had not reached an LDL-C level of <70 mg/dL (1.81 mmol/L) or <100 mg/dL (2.59 mmol/L), respectively, and on atorvastatin 10 mg/day. Mean baseline LDL-C levels were 102 mg/dL (2.64 mmol/L). Twenty-two patients (2%) discontinued treatment due to an adverse event.

The primary endpoint was percent change in LDL-C from baseline to week 6. Efficacy was evaluated for all patients who had at least one dose of study medication, had a baseline measurement and at least one post-baseline measurement (modified ITT). Ezetimibe added to atorvastatin (equivalent to ZETEZE 10/10) significantly reduced LDL-C from baseline after 6 weeks of treatment compared with doubling the dose of atorvastatin from 10 to 20 mg (-26.7% vs -12.8%; p<0.001). Additionally, treatment with ZETEZE 10/10 resulted in a significantly greater percentage of patients achieving LDL-C <100 mg/dL (2.59 mmol/L) for high risk patients without AVD and <70 mg/dL (1.81 mmol/L) for high risk patients with AVD after 12 weeks of treatment, compared to the group that had atorvastatin increased to 40 mg at week 6 (49.4% vs. 39.3%, p<0.001).

Switching Study

In a multicentre, double-blind, controlled, 12-week, 2-phase study (P162), 1539 high-cardiovascular-risk patients, with a LDL-C level between 2.6 mmol/L and 4.1 mmol/L (100 and 160 mg/dL) at baseline, on atorvastatin 10 mg daily were randomised to one of three treatment groups: two of which were atorvastatin 20 mg or ZETEZE 10/10. After 6 weeks of treatment (Phase I), based on a random allocation schedule established at the start of Phase I, patients taking atorvastatin 20 mg who failed to achieve a LDL-C level < 2.6 mmol/L (100 mg/dL) were switched to either atorvastatin 40 mg or ZETEZE 10/20 for 6 weeks (Phase II)ZETEZE. Reductions in LDL-C and comparisons between the ZETEZE group and other treatment groups studied are shown in Table 5.

Table 5

Response to ZETEZE (Co-administration of Ezetimibe and Atorvastatin) in High-Risk Patients with a LDL-C Level Between 2.6 mmol/L and 4.1 mmol/L (100 and 160 mg/dL) on Atorvastatin 10 mg Daily at Baseline

Treatment	**N**	**Percent Change from Baseline**[†]					
		Total-C	LDL-C	Apo B	TG[‡]	HDL-C	Non-HDL-C
Phase I Switched from atorvastatin 10 mg							
ZETEZE 10/10	120	-13.5	-22.2	-11.3	-6.0	+0.6	-18.3
Atorvastatin 20 mg	480	-6.4[§]	-9.5[§]	-6.0[¶]	-3.9	-1.1	-8.1[§]
Phase II Switched from							

atorvastatin 20 mg							
ZETEZE 10/20	124	-10.7	-17.4	-9.8	-5.9	+0.7	-15.1
Atorvastatin 40 mg	124	-3.8 Þ	-6.9 Þ	-5.4	-3.1	+1.7	-5.8 Þ

† M-Estimates (based on the method of Huber; 95% CI and p-value were obtained from fitting a robust Regression model with terms for treatment and baseline)
‡ Geometric mean percent changes from baseline in TG were calculated based on back-transformation via exponentiation of the model-based least square (LS) means and expressed as (geometric mean – 1) multiplied by 100
§ p<0.001 versus ZETEZE 10/10
¶ p<0.01 versus ZETEZE 10/10
ZETEZE Þ p<0.001 versus ZETEZE 10/20

Table 5 does not contain data comparing the effects of ZETEZE 10/10 or 10/20 to doses higher than atorvastatin 40 mg.

Long term studies

A 12-month, blinded comparator study (P2154) enrolled 246 (101 male, 145 female) subjects who had completed study P0692. Patients in this follow-on study were aged from 26 to 86 years, with primary hypercholesterolaemia. Mean baseline LDL-C was 184.6 and 180.6 mg/dL (4.78 and 4.68 mmol/L) in the atorvastatin monotherapy and co-administration groups respectively. A greater proportion of subjects in the monotherapy group had a medical history or physical finding of cardiovascular disease (31% vs. 19%) and were hypertensive (42% vs. 34%) compared to the co-administration group. Forty-one subjects discontinued treatment; 22 discontinued due to adverse events (3/45 in the monotherapy group and 19/201 in the co-administration group).

Patients were initially dosed with either double-blind ezetimibe 10 mg or matching placebo co-administered with open-label atorvastatin 10 mg once daily in the morning. After at least 6 weeks, the atorvastatin dose could be titrated up incrementally to a maximum of 80 mg once daily to achieve the subject's NCEP ATP II target LDL-C level. Efficacy evaluations were performed on all subjects in the follow-up study who had at least one post-baseline lipid measurement (modified ITT). Overall, co-administration of ezetimibe and atorvastatin (equivalent to ZETEZE) reduced LDL-C levels during this 12-month study significantly more than atorvastatin monotherapy. At week 6 (the first time point assessed), LDL-C was reduced from baseline by approximately 37% in the atorvastatin monotherapy group and by approximately 53% in the ZETEZE group. The LDL-C-lowering effect was seen by six weeks of treatment and maintained during the 12-month double-blind study period.

A 12-month, open-label study (P1418) was conducted in patients with HeFH, known CHD or multiple cardiovascular risk factors (≥2) who were not controlled by a starting dose of atorvastatin 10 mg and had successfully completed a 14-week double-blind efficacy and safety study (P00693). Four hundred and thirty-two hypercholesterolaemic patients (56% male) with mean age 52 years (range 18 to 82 years) and mean baseline LDL-C 187 mg/dL (4.84 mmol/L) received open-label ezetimibe 10 mg co-administered with atorvastatin 10 mg (equivalent to ZETEZE 10/10) at the beginning of the study, with up titration of atorvastatin to reach target LDL-C. Eighty-nine percent of patients had a cardiovascular risk factor or family history of cardiovascular disease. Approximately 38% had a history of hypertension

and 26% had angina pectoris. Thirty-four subjects discontinued from the follow-on study, 12 due to adverse events.

Efficacy evaluations were carried out on all subjects in the follow-on study who had at least one post-baseline lipid measurement (modified ITT). Over the 12-month study period, ZETEZE 10/10-10/80 was effective in achieving and maintaining a reduction in LDL-C. The mean LDL-C value at study end was reduced by 30% from the parent study baseline. Reductions were noted as of Month 1, were slightly greater at Month 3 and were maintained at similar levels throughout the study period. Commensurate reductions in TC were observed, and reductions in TG, and an increase in HDL-C, were also noted over time.

Homozygous Familial Hypercholesterolaemia (HoFH)

A double-blind, randomised, 12 week study (P1030) was performed in 50 patients (21 male, 29 female, aged 11 to 74 years of age) with a clinical and/or genotypic diagnosis of HoFH. Baseline LDL-C concentrations ranged from 116 to 652 mg/dL (3.00 to 16.89 mmol/L) (mean: 346 mg/dL [8.96 mmol/L] in the monotherapy group; 321 mg/dL [8.31 mmol/L] in the co-administration group). Approximately 74% of subjects had known family history of coronary artery disease and approximately 16% had some degree of hypertension at baseline. Twenty-five subjects received concomitant apheresis or plasmapheresis. Two subjects discontinued treatment early due to adverse events considered to be unrelated to study treatment.

Data were analysed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline (ITT). The primary endpoint was the percent change from baseline in direct LDL-C concentration at week 12. Increasing the dose of atorvastatin from 40 to 80 mg (n=12) produced a reduction of LDL-C of 2% from baseline on atorvastatin 40 mg. Co-administered ezetimibe and atorvastatin equivalent to ZETEZE (10/40 and 10/80 pooled, n=24), produced a reduction of LDL-C of 19% from baseline on atorvastatin 40 mg. In those patients co-administered ezetimibe and atorvastatin equivalent to ZETEZE (10/80 mg, n=12), a reduction of LDL-C of 25% from baseline on atorvastatin 40 mg was produced.

After completing the 12 week study, eligible patients (n=35), who were receiving atorvastatin 40 mg at baseline, were assigned to co-administered ezetimibe and atorvastatin equivalent to ZETEZE 10/40 for up to an additional 24 months (P1417). Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg. One patient discontinued treatment due to a drug related adverse event. At the end of the 24 months, ZETEZE (10/40 and 10/80 mg pooled) produced a reduction of 18% in LDL-C that was consistent with that seen in the 12-week study (modified ITT analysis – included patients who completed 24 months of treatment).

<u>Ezetimibe</u>

In two multicentre, double-blind, placebo-controlled, 12-week studies in 1,719 patients with primary hypercholesterolaemia, ezetimibe significantly lowered total-C (-13%), LDL-C (-19%), Apo B (-14%), and TG (-8%), and increased HDL-C (+3%) compared to placebo. Reduction in LDL-C was consistent across age, sex, race and baseline LDL-C. In addition, ezetimibe 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.

Atorvastatin

Prevention of Cardiovascular Disease

In a placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the effect of atorvastatin 10 mg on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients, 40-80 years old, with TC levels ≤251 mg/dL (6.5 mmol/L) and at least three cardiovascular risk factors. Patients were followed for a median duration of 3.3 years. Atorvastatin 10 mg significantly (p=0.0005) reduced the rate of coronary events (either fatal coronary heart disease [46 events in the placebo group vs. 40 events in the atorvastatin group] or nonfatal MI [108 events in the placebo group vs. 60 events in the atorvastatin group]) by 36% (based on incidences of 1.9% for atorvastatin vs. 3.0% for placebo).

Although this difference was statistically significant for the whole trial population, this difference was not statistically significant in specified subgroups such as diabetes, patients with left ventricular hypertrophy (LVH), previous vascular disease or metabolic syndrome.

There was no statistically significant reduction in the rate of total mortality, cardiovascular mortality or heart failure in the atorvastatin treated group compared to placebo.

Experience in non-Caucasians is limited and does not permit a precise estimate of the magnitude of the effects of ZETEZE.

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.

INDICATIONS

Primary Hypercholesterolaemia

ZETEZE 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 atorvastatin or ezetimibe alone; or
- already treated with atorvastatin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)

ZETEZE is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

CONTRAINDICATIONS

- Hypersensitivity to any component of this medication.
- Myopathy secondary to other lipid lowering agents

- Active liver disease or unexplained persistent elevations of serum transaminases (see PRECAUTIONS).
- Pregnancy and lactation (See PRECAUTIONS). Women of childbearing potential, unless on an effective contraceptive and highly unlikely to conceive.
- ZETEZE in combination with fenofibrate is contraindicated in patients with gall bladder disease.
- Concomitant use with fusidic acid (see PRECAUTIONS and INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

No incremental benefit of Zeteze on cardiovascular morbidity and mortality over and above that demonstrated for atorvastatin has been established. A beneficial effect of ezetimibe on cardiovascular morbidity or mortality has not been demonstrated.

Liver Enzymes

As with other lipid-lowering agents of the same class, moderate (>3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin.

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2, 0.2, 0.6, and 2.3% for 10, 20, 40, and 80mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

In controlled clinical studies, the incidence of consecutive elevations (³ 3 X the upper limit of normal [ULN]) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled co-administration trials in patients receiving ezetimibe with atorvastatin, the incidence of consecutive elevations (³ 3 X ULN) in hepatic transaminase levels was 0.6% for patients treated with ezetimibe administered with atorvastatin (See ADVERSE EFFECTS).

Liver function tests should be performed before the initiation of treatment and periodically thereafter. There have been rare postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

ZETEZE should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of ZETEZE (see CONTRAINDICATIONS).

Hepatic Insufficiency

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

Skeletal Muscle

Ezetimibe

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.

Atorvastatin

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like other statins, occasionally causes myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times ULN. The concomitant use of higher doses of atorvastatin with certain drugs such as cyclosporin and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with statin use. IMNM is characterised by: proximal muscle weakness and elevated serum creatinine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. ZETEZE therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with statins is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, clarithromycin, combinations of HIV protease inhibitors, including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, azole antifungals, colchicine, or hepatitis-C protease inhibitors

(e.g.telaprevir, boceprevir) (see INTERACTIONS WITH OTHER MEDICINES). Physicians considering combined therapy with ZETEZE and fibric acid derivatives, erythromycin, clarithromycin, a combination of saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, azole antifungals, colchicine, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of ZETEZE should be considered when taken concomitantly with the aforementioned drugs. (See DOSAGE ADMINISTRATION, Use in Combination with Other Medicinal Compounds) Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Prescribing recommendations for interacting agents are summarized in Table 6 (see DOSAGE AND ADMINISTRATION, Cyclosporin, Clarithromycin, Itraconazole, or Certain Protease Inhibitors, and INTERACTIONS WITH OTHER MEDICINES, CYP3A4Interactions).

Table 6
Atorvastatin Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations for ZETEZE
Cyclosporin, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir), gemfibrozil	Avoid ZETEZE.
Other fibrates (except fenofibrate), fusidic acid	Not recommended with ZETEZE
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary.
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir), hepatitis C protease inhibitor (boceprevir)	Do not exceed 10/20 mg ZETEZE daily.
HIV protease inhibitor (nelfinavir)	Do not exceed 10/40 mg ZETEZE daily.

* Use with caution and with the lowest dose necessary

There have been reports of rhabdomyolysis (including some fatalities) in patients receiving concomitant fusidic acid and statins (see CONTRAINDICATIONS and INTERACTIONS WITH OTHER MEDICINES). In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of the fusidic acid treatment. The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

ZETEZE therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (e.g. severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

Fibrates

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied. Therefore, co-administration of ZETEZE and fibrates is 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 TRIALS and ADVERSE EFFECTS sections), co-administration of ZETEZE and fenofibrate is not recommended in patients with pre-existing gallbladder disease (see CONTRAINDICATIONS).

Cyclosporin

In patients taking cyclosporine, therapy with ZETEZE should be avoided (See Table 6, INTERACTIONS WITH OTHER MEDICINES and DOSAGE AND ADMINISTRATION).

Anticoagulants

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

Haemorrhagic Stroke

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed a higher incidence of haemorrhagic stroke in patients on atorvastatin 80 mg (55/2365, 2.3%) compared to placebo (33/2366, 1.4%), (p=0.02). Throughout the study, all cause mortality was numerically higher in the atorvastatin arm than the placebo arm. At study end all cause mortality was 9.1% on atorvastatin vs. 8.9 % on placebo.

The increased risk of haemorrhagic stroke was observed in patients who entered the study with prior haemorrhagic stroke (15.6% for atorvastatin vs. 4.2 % for placebo, HR 4.06; 95% CI 0.84-19.57) or prior lacunar infarct (2.8% for atorvastatin vs. 0.6% for placebo, HR 4.99; 95%CI 1.71-14.61). All cause mortality was also increased in these patients with prior haemorrhagic stroke (15.6% for atorvastatin vs. 10.4% for placebo) or prior lacunar infarct (10.9% for atorvastatin vs. 9.1% for placebo). The potential risk of haemorrhagic stroke should be carefully considered before initiating treatment with ZETEZE in patients with recent (1-6 months) stroke or TIA.

In 68% of patients who entered the study with neither a haemorrhagic stroke nor lacunar infarct, the risk of haemorrhagic stroke on atorvastatin vs. placebo was 2% vs. 1.8 % (large vessel), 1.7% vs. 1.6 % (TIA), 1.6% vs. 1.7 % (unknown cause).

Endocrine Function

Statins interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if ZETEZE is administered concomitantly with other drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including atorvastatin.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see ADVERSE EFFECTS). 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, ZETEZE therapy should be discontinued.

Effects on Fertility

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.

Atorvastatin

The effects of atorvastatin on spermatogenesis and human fertility have not been investigated in clinical studies. Dietary administration of 100 mg atorvastatin/kg/day to rats caused a decrease in spermatid concentration in the testes, a decrease in sperm motility and an increase in sperm abnormalities. Similar effects, however, were not observed in male rats dosed by gavage to 175 mg/kg/day (plasma AUC for HMG-CoA reductase inhibitory activity 14 times higher than in humans dosed at 80 mg/day) and male fertility was not affected in either study. No adverse effects on fertility or reproduction were observed in female rats given doses up to 225 mg/kg/day (plasma AUC for enzyme inhibitory activity 56 times higher than in humans dosed at 80 mg/day). Atorvastatin caused no adverse effects on sperm or semen parameters, or on reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for 2 years (Plasma AUC for enzyme inhibitory activity 13 times higher than in humans).

Use in Pregnancy

Pregnancy Category D

The definition of Pregnancy Category D is 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.

ZETEZE 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).

ZETEZE 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 in combination with statins, including atorvastatin, 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.

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.

Atorvastatin

Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause foetal harm when administered to pregnant women.

HMG-CoA reductase inhibitors are contraindicated in pregnancy. The risk of foetal injury outweighs the benefits of HMG-CoA reductase inhibitor therapy during pregnancy.

Atorvastatin crosses the rat placenta and reaches a level in foetal liver equivalent to that in maternal plasma. Animal reproduction studies showed no evidence of teratogenic activity in rats or rabbits at oral doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. Increased post-implantation loss, decreased foetal weight and increased skeletal variations were observed in rats dosed at 100–300 mg/kg/day and rabbits dosed at 50–100 mg/kg/day. In a peri/post natal study, rats dosed at 225 mg/kg/day showed an increased incidence of stillbirths, decreases in birthweight, an increased incidence of dilated renal pelvis, increased postnatal mortality, suppression of pup growth, retardation of physical development and abnormal behavioural development; some of these effects were also observed at the non-maternotoxic dose of 100 mg/kg/day; the plasma AUC for HMG-CoA reductase inhibitory activity at the no effect dose level of 20 mg/kg/day was similar to that in humans dosed at 80 mg/day.

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 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 atorvastatin.

Studies in rats have shown that ezetimibe and atorvastatin are excreted in milk. It is not known whether ezetimibe or atorvastatin are excreted into human breast milk, therefore, women who are breast feeding should not take ZETEZE (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.

In rats, plasma concentrations of atorvastatin are similar to those in milk.

Paediatric Use

There are insufficient data for the safe and effective administration of ZETEZE in paediatric patients.

Use in the Elderly

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

Co-administration of ezetimibe and atorvastatin was studied in 1053 patients ≥ 65 years of age with hypercholesterolaemia and high risk for CHD. Patients received ezetimibe 10 mg and atorvastatin doses from 10 to 40 mg daily. The treatments were well tolerated, with a similar safety profile to that observed in younger patients.

Atorvastatin

Treatment experience in adults aged ≥70 years with doses of atorvastatin up to 80 mg/day has been evaluated in 221 patients. The safety and efficacy of atorvastatin in this population were similar to those of patients <70 years of age.

Genotoxicity

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.

Atorvastatin

Atorvastatin did not demonstrate mutagenic or clastogenic potential in an appropriate battery of assays. It was negative in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, and in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells. Atorvastatin did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay and was negative in the *in vivo* mouse micronucleus test.

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 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.

Atorvastatin

In a 2-year study in rats given 10, 30 or 100 mg/kg/day, the incidence of hepatocellular adenoma was marginally, although not significantly, increased in females at 100 mg/kg/day. The maximum dose used was 11 times higher than the highest human dose (80 mg/kg) based on AUC (0–24) values. In a 2-year study in mice given 100, 200, or 400 mg/kg, incidences of hepatocellular adenoma in males and hepatocellular carcinoma in females were increased at 400 mg/kg. The maximum dose used was 14 times higher than the highest human dose (80 mg/kg) based on AUC (0-24) values. Other HMG-CoA reductase inhibitors have been reported to induce hepatocellular tumours in mice and rats.

Effect on Ubiquinone Levels (COQ_{10})

Significant decreases in circulating ubiquinone levels in patients treated with atorvastatin and other statins have been observed. The clinical significance of a potential long-term, statin-induced deficiency of ubiquinone has not been established.

Effect on Lipoprotein (a)

Like other HMG-CoA reductase inhibitors, atorvastatin has variable effects on lipoprotein (a) (Lp (a)). It is unclear whether the beneficial effects of lowering LDL-C and total cholesterol in some patients may be blunted by raised Lp (a) levels.

Effect on Laboratory Tests

ZETEZE can cause elevations in ALT/AST, alkaline phosphatase, GGT, bilirubin and creatine kinase.

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 ZETEZE may affect some patients' ability to drive or operate machinery. Individual responses to ZETEZE may vary (see ADVERSE EFFECTS).

INTERACTIONS WITH OTHER MEDICINES

No clinically significant pharmacokinetic interaction was seen when ezetimibe was co-administered with atorvastatin.

Cytochrome P450

Inhibitors of 3A4

Atorvastatin

Concomitant administration of atorvastatin with inhibitors of cytochrome P450 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and

potentiation of effects depends on the variability of effect on cytochrome P450 3A4. Pharmacokinetic drug interactions that result in increased systemic concentration of atorvastatin have been noted with HIV protease inhibitors (fosamprenavir and combinations of lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, fosamprenivir/ritonavir), hepatitis C protease inhibitors (boceprevir), clarithromycin and itraconazole. In patients taking cyclosporin, the HIV protease inhibitor tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of ZETEZE should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing ZETEZE and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir or fosamprenivir plus ritonavir, or the hepatitis C protease inhibitor boceprevir, the dose of ZETEZE should not exceed 10/20 mg and should be used with caution (see PRECAUTIONS, Skeletal Muscle and DOSAGE and ADMINISTRATION, Cyclosporin, Clarithromycin, Itraconazole or Certain Protease Inhibitors). In patients taking the HIV protease inhibitor nelfinavir, the dose of ZETEZE should not exceed 10/40 mg and close clinical monitoring is recommended. Based on experience with other HMG-CoA reductase inhibitors caution should be exercised when atorvastatin is administered with inhibitors of cytochrome P450 3A4 (e.g. macrolide antibiotics including erythromycin and clarithromycin, and azole antifungals including itraconazole). The risk of myopathy during treatment with other HMG-CoA reductase inhibitors is increased with concurrent administration of cyclosporin, fibric acid derivatives, erythromycin, azole antifungals or niacin:

Erythromycin/Clarithromycin: In healthy individuals, co-administration of atorvastatin (10mg QD) and erythromycin (500mg QID), or clarithromycin (500mg BID), known inhibitors of cytochrome P450 3A4, was associated with higher plasma concentrations of atorvastatin. In patients taking clarithromycin the dose of ZETEZE should not exceed 10/20 mg (see PRECAUTIONS, Skeletal Muscle).

Protease Inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Itraconazole: Concomitant administration of atorvastatin (20 to 40mg) and itraconazole (200mg) was associated with an increase in atorvastatin AUC. In patients taking itraconazole the dose of ZETEZE should not exceed 10/20 mg.

Diltiazem Hydrochloride: Co-administration of atorvastatin (40mg) with diltiazem (240mg) was associated with higher plasma concentrations of atorvastatin.

Cimetidine: Atorvastatin plasma concentrations and LDL-C reduction were not altered by co-administration of cimetidine.

Grapefruit Juice: Contains one or more components that inhibit cytochrome P450 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 L per day).

<u>*Ezetimibe*</u>

Cimetidine: Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

Inducers of 3A4

Atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4.

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g. efavirenz, rifampicin, phenytoin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter (OATP1B1), simultaneous co-administration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.

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.

Other Drug Interactions

Ezetimibe

Ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyloestradiol and levonorgestrel), glipizide, tolbutamide or midazolam during co-administration.

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.

Atorvastatin

Co-administration of an oral antacid suspension containing magnesium and aluminium hydroxides with atorvastatin decreased atorvastatin plasma concentrations approximately 35%, however, LDL-C reduction was not altered.

Bile Acid Sequestrants

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

Colestipol

Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

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.

Fibrates

The safety and effectiveness of ezetimibe and atorvastatin administered with fibrates have not been established. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of ezetimibe and atorvastatin with fibrates is not recommended until use in patients is studied.

Fenofibrate

Caution should be used when prescribing ZETEZE and fenofibrate, as fenofibrate can cause myopathy when given alone.

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

Gemfibrozil

Concomitant administration of ZETEZE with gemfibrozil should be avoided.

In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. No clinical data are available.

Anticoagulants

The effect of ZETEZE on the prothrombin time has not been studied.

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 or fluindione. Most of these patients were also on other medications (see PRECAUTIONS).

Atorvastatin

Atorvastatin had no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin treatment.

Fusidic acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. Co-administration 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.

Although interaction studies with atorvastatin and fusidic acid have not been conducted, there have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. If treatment with fusidic acid is necessary, ZETEZE treatment should be discontinued throughout the duration of the fusidic acid treatment (see CONTRAINDICATIONS and PRECAUTIONS, Skeletal Muscle).

Colchicine

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing ZETEZE with colchicine (see PRECAUTIONS).

Transporter Inhibitors

Atorvastatin

Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Inhibitors of the OATP1B1 (e.g. cyclosporin) can increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10mg and cyclosporin 5.2mg/kg/day resulted in an increase in exposure to atorvastatin. The co-administration of ZETEZE with cyclosporin should be avoided (see PRECAUTIONS, Skeletal Muscle and DOSAGE AND ADMINISTRATION).

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).

Digoxin

When multiple doses of digoxin (0.25mg QD) and 10mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, steady-state plasma digoxin concentrations increased by approximately 20% following administration of digoxin with 80mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Oral Contraceptives

Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyloestradiol increased AUC values for norethindrone and ethinyl oestradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking ZETEZE.

Other Medicines shown not to interact with atorvastatin

Amlodipine

Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80mg daily and amlodipine 10mg daily at steady-state. In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80mg and amlodipine 10mg resulted in an 18% increase in exposure to atorvastatin, which was not clinically meaningful.

Azithromycin

Co-administration of atorvastatin 10mg daily and azithromycin (500mg QD) did not alter the plasma concentrations of atorvastatin.

Other concomitant therapy

In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and oestrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with all specific agents have not been conducted.

ADVERSE EFFECTS

Co-administration of ezetimibe and atorvastatin has been evaluated for safety in more than 2,400 patients in 7 clinical trials. Co-administration of ezetimibe and atorvastatin was generally well-tolerated. Table 7 summarises the common (≥ 1.0% in any group) drug-related adverse events by system organ class and preferred term.

Table 7
Drug-related Adverse Events Occurring in ≥1.0% in Patients Receiving Atorvastatin or Co-Administered Ezetimibe and Atorvastatin[a]

	Atorvastatin[a] (%) N=2521	Co-administered ezetimibe and atorvastatin[a] (%) N=2523
Gastrointestinal disorders		
Diarrhoea	0.7	1.0
Musculoskeletal and connective tissue disorders		
Myalgia	1.2	1.5

[a] All doses

In a placebo-controlled clinical trial in 628 patients with hyperlipidaemia (P0692), in which patients were treated for up to 12 weeks, the most commonly reported adverse reactions (incidence ≥2% and greater than placebo) were:

Table 8

Clinical and Selected Laboratory Adverse Reactions Occurring in ≥ 2% of Patients Treated with Co-Administered Ezetimibe and Atorvastatin* and at an Incidence Greater then Placebo, Regardless of Causality

Body System / Organ Class Adverse Reaction	Placebo (%) N=60	Ezetimibe 10 mg (%) N=65	Atorvastatin† (%) N=248	Eze/Atorva† (%) N=255
Nervous system disorders				
Dizziness	0	6	<1	2
Respiratory, thoracic, and mediastinal disorders				
Coughing	0	3	<1	2
Gastrointestinal disorders				
Abdominal pain	2	2	4	3
Nausea	0	2	5	3
Musculoskeletal and connective tissue disorders				
Arthralgia	0	5	6	3
Muscle weakness	0	2	0	2
Musculoskeletal pain	3	8	5	4
Metabolism and nutrition disorders				
Hyperkalaemia	0	0	<1	2

Infections and infestations				
Bronchitis	0	2	2	2
Sinusitis	0	3	2	2
Vascular disorders				
Hot flushes	0	0	<1	2
Investigations				
ALT increased	0	0	2	5
AST increased	0	0	<1	4

* Equivalent to ZETEZE

† All doses

The following other uncommon (≥1/1000, <1/100) drug-related adverse experiences by system organ class and preferred term were reported in patients taking co-administered ezetimibe and atorvastatin:

Infections and Infestations: Uncommon: influenza

Psychiatric disorders: Uncommon: depression, insomnia, sleep disorder

Nervous system disorders: Uncommon: dysgeusia, paraesthesia, dizziness, headache

Respiratory, thoracic and mediastinal disorders: dyspnoea

Cardiac disorders: Uncommon: sinus bradycardia

Vascular disorders: Uncommon: hot flush

Gastrointestinal disorders: Uncommon: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, frequent bowel movements, stomach discomfort, upset stomach, abdominal distension, constipation, dyspepsia, flatulence, gastritis, nausea

Skin and subcutaneous tissue disorders: Uncommon: acne; urticaria

Musculoskeletal and connective tissue disorders: Uncommon: arthralgia, back pain, muscle fatigue, muscular weakness, pain in extremity, muscle spasms, musculoskeletal stiffness

General disorders and administration site conditions: Uncommon: asthenia, oedema, fatigue, malaise

Investigations: Uncommon: ALT and/or AST increased, alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, weight increased, blood CK increased.

Laboratory Values

In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ³ 3 X ULN, consecutive) was 0.6% for patients treated with co-administered ezetimibe and atorvastatin. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy (See PRECAUTIONS).

Persistent increases in serum transaminases >3 x ULN occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2, 0.2, 0.6, and 2.3% for 10, 20, 40, and 80mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

In controlled clinical studies, the incidence of consecutive elevations (³ 3 X the upper limit of normal [ULN]) in hepatic transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

Discontinuations

Gastrointestinal disorders and musculoskeletal and connective tissue disorders contributed to the majority of adverse experiences which lead to discontinuation in clinical trials. A total of 37 (0.7%) of 5169 patients discontinued due to gastrointestinal adverse experiences; 2 (3.3%) of 60 patients in the placebo group, 0 of 65 patients in the ezetimibe monotherapy group, 20 (0.8%) of 2521 patients in the atorvastatin monotherapy group, and 15 (0.6%) of 2523 patients in the ezetimibe + atorvastatin coadministration group. A total of 28 (0.5%) of 5169 patients discontinued due to musculoskeletal adverse experiences; 13 (0.5%) of 2521 patients on atorvastatin monotherapy and 15 (0.6%) of 2523 patients on ezetimibe + atorvastatin. The most frequently reported adverse experiences causing discontinuation were nausea; 7 (0.3%) and 3 (0.1%) patients, respectively, and myalgia, 8 (0.3%) and 8 (0.3%) patients, respectively, in the atorvastatin monotherapy and ezetimibe + atorvastatin treatment groups.

In a ZETEZE (ezetimibe and atorvastatin) placebo-controlled clinical trial, 628 patients (age range 18-86 years, 59% women, 85% Caucasians, 6% Blacks, 5% Hispanics, 3% Asians) with a median treatment duration of 12 weeks, 6% of patients on ZETEZE and 5% of patients on placebo discontinued due to adverse reactions.

The most common adverse reactions in the group treated with ZETEZE that led to treatment discontinuation and occurred at a rate greater than placebo were:

- Myalgia (0.8%)
- Abdominal pain (0.8%)
- Increased hepatic enzymes (0.8%)

Post-marketing Experience and Other Clinical Trial Experience

The following additional adverse reactions have been reported in post-marketing use with co-administered ezetimibe and atorvastatin or in clinical studies or post-marketing use with ezetimibe or atorvastatin. Not all effects listed have been causally associated with ezetimibe or atorvastatin.

Eye disorders: vision blurred

Infections and infestations: nasopharyngitis, urinary tract infection, infection, sinusitis, pharyngitis

Blood and lymphatic system disorders: thrombocytopenia

Immune system disorders: hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria

Metabolism and nutrition disorders: decreased appetite, anorexia, hyperglycaemia; hypoglycaemia

Nervous system disorders: hypoesthesia, dysgeusia, amnesia, peripheral neuropathy

Psychiatric disorders: nightmare

Ear and labyrinth disorders: tinnitus, deafness

Vascular disorders: hypertension, haemorrhagic stroke

Respiratory, thoracic, and mediastinal disorders: cough, pharyngolaryngeal pain, epistaxis, asthma

Gastrointestinal disorders: pancreatitis, gastroesophageal reflux disease, eructation, vomiting, dry mouth

Hepatobiliary disorders: hepatitis, cholelithiasis, cholecystitis, hepatic failure, cholestasis

Skin and subcutaneous tissue disorders: pruritus, skin rash, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrosis), alopecia

Musculoskeletal and connective tissue disorders: immune mediated necrotising myopathy, myopathy/rhabdomyolysis which may be fatal (examples of signs and symptoms are muscle weakness, muscle swelling, muscle pain, dark urine, myoglobinuria, elevated serum creatine kinase, acute renal failure and cardiac arrhythmia (See PRECAUTIONS), neck pain, joint swelling, musculoskeletal pain, myositis

Reproductive system and breast disorders: gynaecomastia, erectile dysfunction

General disorders and administration site conditions: chest pain, pain, oedema peripheral, pyrexia

Injury, poisoning and procedural complications: tendon rupture, injury

Investigations: white blood cells urine positive

The following adverse events have been reported with some statins:

- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see PRECAUTIONS)
- Diabetes mellitus: frequency will depend on the presence or absence of risk factors (fasting blood glucose $\geq$ 5.6 mmol/L, BMI > 30kg/m^2, raised triglycerides, history of hypertension)

A post-hoc analysis of a clinical study (SPARCL) in patients without known coronary heart disease who had a recent stroke or TIA, showed an increased risk of haemorrhagic stroke in patients with prior haemorrhagic stroke or prior lacunar infarct (see PRECAUTIONS).

In ASCOT (see CLINICAL TRIALS, Prevention of Cardiovascular Disease) involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up.

There has been rare postmarketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These

cognitive issues have been reported for all statins. The reports are generally non-serious, and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

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 (PY) 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.

Please see the individual Product Information documents for atorvastatin and ezetimibe for further information on adverse effects.

DOSAGE AND ADMINISTRATION

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

Patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ZETEZE.

ZETEZE can be administered within the dosage range of 10/10 mg to 10/80 mg as a single daily dose. The recommended starting dose of ZETEZE 10/10 mg or 10/20 mg once daily. ZETEZE can be administered at any time of the day, with or without food. Therapy should be individualised according to the target lipid levels, the recommended goal of therapy, and the patient's response. After initiation and/or upon titration of ZETEZE, lipid levels should be re-analysed within 2 or more weeks and dosage adjusted according to the patient's response.

Advice to Patients Currently Taking Ezetimibe and/or Atorvastatin

To prevent accidental excessive dosing due to inadvertent duplication of administration of ezetimibe and/or atorvastatin, patients currently taking ezetimibe and/or atorvastatin should be advised that ZETEZE replaces these medications and therefore the current ezetimibe and/or atorvastatin medication(s) should no longer be taken. Patients should also be advised to take any remaining medication(s) to the pharmacy for appropriate disposal.

Dosage in Patients with Homozygous Familial Hypercholesterolaemia (HoFH)

The dosage of ZETEZE in patients with homozygous familial hypercholesterolemia is 10/40 mg or 10/80 mg daily. ZETEZE should be used as an adjunct to other treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Renal Insufficiency

No dosage adjustment is required for renally impaired patients.

Hepatic insufficiency

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh A or score 5 to 6). Treatment with ZETEZE is not recommended in patients with moderate (Child Pugh B or score 7 to 9) or severe (Child Pugh C or score > 9) liver dysfunction. The benefits of therapy should be weighed against the risks when ZETEZE is to be given to patients with hepatic insufficiency (see PHARMACOLOGY; CONTRAINDICATIONS, and PRECAUTIONS)

Use in Combination with Other Medicinal Compounds

Bile Acid Sequestrants

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

Cyclosporin, Clarithromycin, Itraconazoleor Certain Protease Inhibitors

In patients taking cyclosporin or the HIV protease inhibitors tipranavir plus ritonavir or the hepatitis C protease inhibitor telaprevir, therapy with ZETEZE should be avoided. In patients with HIV taking lopinavir plus ritonavir, caution should be used when prescribing ZETEZE and the lowest dose necessary employed. In patients taking clarithromycin, itraconazole, or the hepatitis C protease inhibitor boceprevir, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with ZETEZE should be limited to 10/20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir, therapy with ZETEZE should be limited to 10/40 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of ZETEZE is employed (see PRECAUTIONS, Skeletal muscle and INTERACTIONS WITH OTHER MEDICINES).

Use in the Elderly

No dosage adjustment is required for elderly patients for ZETEZE (See PHARMACOLOGY, Characteristics in Patients, (Special Populations).

Paediatric Use

Treatment with ZETEZE is not recommended.

OVERDOSAGE

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of an overdose.

No specific treatment of overdosage with ZETEZE 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, 40 mg/day to 18 patients with primary hypercholesterolaemia for up to 56 days was generally well tolerated.

A few cases of overdosage have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious.

Atorvastatin

If there has been significant ingestion, consider administration of activated charcoal. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. For rhabdomyolysis, administer sufficient 0.9% saline to maintain urine output of 2 to

3mL/kg/hr. Diuretics may be necessary to maintain urine output. Urinary alkalinisation is not routinely recommended. Due to extensive drug binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

PRESENTATION AND STORAGE CONDITIONS

ZETEZE 10/10 contains 10 mg of ezetimibe and 10.9 mg of atorvastatin calcium trihydrate, equivalent to 10 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 257 on one side and plain on the other.

ZETEZE 10/20 contains 10 mg of ezetimibe and 21.7 mg of atorvastatin calcium trihydrate, equivalent to 20 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 333 on one side and plain on the other.

ZETEZE 10/40 contains 10 mg of ezetimibe and 43.4 mg of atorvastatin calcium trihydrate, equivalent to 40 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 337 on one side and plain on the other.

ZETEZE 10/80 contains 10 mg of ezetimibe and 86.8 mg of atorvastatin calcium trihydrate, equivalent to 80 mg of atorvastatin. The tablets are white to off-white capsule-shaped, biconvex, film-coated with code 357 on one side and plain on the other.

Available as 10 (starter) and 30 tablet blister (aluminium/aluminium) packs.

Store below 30°C and in a dry place.

NAME AND ADDRESS OF THE 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 ARTG

4th February 2015

DATE OF MOST RECENT AMENDMENT

21st January 2015

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