Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atozet 10 mg/10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of ezetimibe and 10 mg of atorvastatin (as atorvastatin calcium trihydrate).

Excipient(s) with known effect:
Each 10 mg/10 mg film-coated tablet contains 153 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

10 mg/10 mg tablet: Capsule-shaped, biconvex, white to off-white, film-coated, size 12.74 mm x 5.10 mm, "257" debossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Cardiovascular Events
ATOZET is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not.

Hypercholesterolaemia
ATOZET is indicated as adjunctive therapy to diet for use in adults with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate.

- patients not appropriately controlled with a statin alone
- patients already treated with a statin and ezetimibe

Homozygous Familial Hypercholesterolaemia (HoFH)
ATOZET is indicated as adjunctive therapy to diet for use in adults with HoFH. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).

4.2 Posology and method of administration

Posology
Hypercholesterolaemia and/or Coronary Heart Disease (with ACS History)
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with ATOZET.

The dose range of ATOZET is 10/10 mg/day through 10/80 mg/day. The typical dose is 10/10 mg once a day. The patient's low-density lipoprotein cholesterol (LDL-C) level, coronary heart disease risk status, and response to current cholesterol-lowering therapy should be considered when starting therapy or adjusting the dose.

The dose of ATOZET should be individualised based on the known efficacy of the various dose strengths of ATOZET (see section 5.1, Table 4) and the response to the current cholesterol-lowering therapy. Adjustment of dose should be made at intervals of 4 weeks or more.

Homozygous Familial Hypercholesterolaemia
The dose of ATOZET in patients with homozygous FH is 10/10 to 10/80 mg daily. ATOZET may be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

Co-administration with other medicines
Dosing of ATOZET should occur either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with ATOZET, the dose of ATOZET should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

Elderly
No dose adjustment is required for older patients (see section 5.2).

Paediatric population
The safety and efficacy of ATOZET in children has not been established (see section 5.2). No data are available.

Hepatic impairment
ATOZET should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). ATOZET is contraindicated in patients with active liver disease (see section 4.3).

Renal impairment
No dose adjustment is required for renally impaired patients (see section 5.2).

Method of administration
ATOZET is for oral administration. ATOZET can be administered as a single dose at any time of the day, with or without food.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Therapy with ATOZET is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

ATOZET is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN).

ATOZET is contraindicated in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

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

ATOZET contains atorvastatin. Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine phosphokinase (CPK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria, which may lead to renal failure.

Before the treatment
ATOZET should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CPK level should be measured before starting treatment in the following situations:

- renal impairment,

- hypothyroidism,
- personal or familial history of hereditary muscular disorders,
- previous history of muscular toxicity with a statin or fibrate,
- previous history of liver disease and/or where substantial quantities of alcohol are consumed,
- in elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis,
- situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2).

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.

If CPK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine phosphokinase measurement

Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.

Whilst on treatment

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever or if muscle signs and symptoms persist after discontinuing ATOZET.
- If such symptoms occur whilst a patient is receiving treatment with ATOZET, their CPK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CPK levels are elevated to ≤ 5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of ATOZET or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.
- ATOZET must be discontinued if clinically significant elevation of CPK levels (> 10 times ULN) occur, or if rhabdomyolysis is diagnosed or suspected.
- There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

Due to the atorvastatin component of ATOZET, the risk of rhabdomyolysis is increased when ATOZET is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc.). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, or niacin. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products (see section 4.8).

In cases where co-administration of these medicinal products with ATOZET is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of ATOZET is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of ATOZET should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in

patients receiving fusidic acid and statins in combination (see section 4.5). 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.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of ATOZET and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Daptomycin

Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) co-administered with daptomycin. Caution should be used when prescribing HMG-CoA reductase inhibitors with daptomycin, as either agent can cause myopathy and/or rhabdomyolysis when given alone. Consideration should be given to temporarily suspend ATOZET in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. Consult the prescribing information of daptomycin to obtain further information about this potential interaction with HMG-CoA reductase inhibitors (e.g. atorvastatin and ezetimibe/atorvastatin) and for further guidance related to monitoring (See section 4.5.).

Myasthenia gravis and ocular myasthenia

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). ATOZET should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Liver Enzymes

In controlled co-administration trials in patients receiving ezetimibe and atorvastatin, consecutive transaminase elevations (≥ 3 times the upper limit of normal [ULN]) have been observed (see section 4.8).

Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the ULN persist, reduction of dose or withdrawal of ATOZET is recommended.

ATOZET should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

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 (see section 5.2).

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established; therefore, co-administration of ATOZET and fibrates is not recommended (see section 4.5).

Ciclosporin

Caution should be exercised when initiating ATOZET in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ATOZET and ciclosporin (see section 4.5).

Anticoagulants

If ATOZET is added to warfarin, another coumarin anticoagulant, or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section 4.5).

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischaemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). 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, statin therapy should be discontinued.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Excipients

ATOZET contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

ATOZET contains less than 1 mmol (23 mg) sodium per tablet and is considered to be essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Multiple mechanisms may contribute to potential interactions with HMG Co-A reductase inhibitors. Drugs or herbal products that inhibit certain enzymes (e.g. CYP3A4) and/or transporter (e.g., OATP1B) pathways may increase atorvastatin plasma concentrations and may lead to an increased risk of myopathy/rhabdomyolysis.

Consult the prescribing information of all concomitantly used drugs to obtain further information about their potential interactions with atorvastatin and/or the potential for enzyme or transporter alterations and possible adjustments to dose and regimens.

Pharmacodynamic interactions

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of ATOZET with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).

Pharmacokinetic interactions

ATOZET

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

Effects of other medicinal products on ATOZET

Ezetimibe

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

Cholestyramine: Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ATOZET to cholestyramine may be lessened by this interaction (see section 4.2).

Ciclosporin: In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/minon a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population, receiving ezetimibe alone, from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medicinal products demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of ciclosporin on Day 7 resulted in a mean 15% increase in ciclosporin AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating ATOZET in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving ATOZET and ciclosporin (see section 4.4).

Fibrates: Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold, respectively. Although these increases are not considered clinically significant, co-administration of ATOZET with fibrates is not recommended (see section 4.4).

Atorvastatin

CYP3A4 inhibitors: Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g., ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with ATOZET cannot be avoided, lower starting and maximum doses of ATOZET should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g., erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with ATOZET may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of ATOZET should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

Inhibitors of Breast Cancer Resistant Protein (BCRP): Concomitant administration of products that are inhibitors of BCRP (e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy; therefore a dose adjustment of atorvastatin should be considered depending on the prescribed dose. Co-administration of elbasvir and grazoprevir with atorvastatin increases plasma concentrations of atorvastatin 1.9-fold (see Table 1); therefore, the dose of ATOZET should not exceed 10/20 mg daily in patients receiving concomitant medications with products containing elbasvir or grazoprevir (see sections 4.2 and 4.4).

Inducers of cytochrome P450 3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampicin, St. John's Wort) 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 ATOZET with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampicin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors: Inhibitors of transport proteins (e.g., ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction of ATOZET and clinical monitoring for efficacy is recommended (see Table 1).

Gemfibrozil / fibric acid derivatives: The use of fibrates alone is occasionally associated with muscle-related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin.

Ezetimibe: The use of ezetimibe alone is associated with muscle-related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid: The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment. **Also see section 4.4.**

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 atorvastatin with colchicine.

Daptomycin: The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors and daptomycin. Consideration should be given to suspending ATOZET temporarily in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk (see section 4.4).

Boceprevir: Exposure to atorvastatin was increased when administered with boceprevir. When co-administration with ATOZET is required, starting with the lowest possible dose of ATOZET should be considered with titration up to desired clinical effect while monitoring for safety, without exceeding a daily dose of 10/20 mg. For patients currently taking ATOZET, the dose of ATOZET should not exceed a daily dose of 10/20 mg during co-administration with boceprevir.

Effects of ATOZET on the pharmacokinetics of other medicinal products

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.

Anticoagulants: Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ATOZET is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Atorvastatin

Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives: Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethisterone and ethinyl estradiol.

Warfarin: In a clinical study in patients receiving chronic warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing, which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting ATOZET in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of ATOZET is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Table 1

Effect of Co-administered Medicinal Products on the Pharmacokinetics of Atorvastatin

Co-administered Medicinal Product and Dosing Regimen	Atorvastatin		ATOZET
	Dose (mg)	Change in AUC[a]	Clinical Recommendation[#]
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (Days 14 to 21)	40 mg on Day 1, 10 mg on Day 20	↑ 9.4 fold	In cases where co-administration with ATOZET is necessary, do not exceed 10/10 mg ATOZET daily. Clinical monitoring of these patients is recommended.
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑ 8.7 fold	
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑ 5.9 fold	In cases where co-administration with ATOZET is necessary, lower maintenance doses of ATOZET are recommended. At ATOZET doses exceeding 10/20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑ 4.4 fold	
Saquinavir 400 mg BID/ Ritonavir 300 mg BID from Days 5-7, increased to 400 mg BID on Day 8), Days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑ 3.9 fold	In cases where co-administration with ATOZET is necessary, lower maintenance doses of ATOZET are recommended. At ATOZET doses exceeding 10/40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑ 3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑ 3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑ 2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑ 2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑ 1.7 fold^	No specific recommendation.
Grapefruit juice, 240 mL OD*	40 mg SD	↑ 37%	Concomitant intake of large quantities of grapefruit juice and ATOZET is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg SD	↑ 51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg SD	↑ 33%^	Lower maximum dose and clinical monitoring of these patients is recommended.

Amlodipine 10 mg, single dose	80 mg SD	↑ 18%	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	↓ less than 1%^	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓ 35%^	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓ 41%	No specific recommendation.
Rifampicin 600 mg OD, 7 days (co-administered)	40 mg SD	↑ 30%	If co-administration cannot be avoided, simultaneous co-administration of ATOZET with rifampicin is recommended, with clinical monitoring.
Rifampicin 600 mg OD, 5 days (doses separated)	40 mg SD	↓ 80%	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	Not recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	↑ 3%	Not recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	↑ 2.3 fold	Lower starting dose and clinical monitoring of these patients is recommended. The dose of ATOZET should not exceed a daily dose of 10/20 mg during co-administration with boceprevir.
Elbasvir 50 mg OD/Grazoprevir 200 mg OD, 13 days	10 mg SD	↑1.94 fold	The dose of ATOZET should not exceed a daily dose of 10/20 mg during co-administration with products containing elbasvir or grazoprevir.
Glecaprevir 400 mg OD/Pibrentasvir 120 mg OD, 7 days	10 mg OD for 7 days	↑ 8.3 fold	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).
[#] See sections 4.4 and 4.5 for clinical significance.
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 mL glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).
^ Total atorvastatin equivalent activity
Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily

Table 2
Effect of Atorvastatin on the Pharmacokinetics of Co-administered Medicinal Products

Atorvastatin and Dosing Regimen	Co-administered Medicinal Product		ATOZET
	Medicinal Product/Dose (mg)	Change in AUC[&]	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑ 15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months -norethisterone 1 mg -ethinyl estradiol 35 microgram	 ↑ 28% ↑ 19%	No specific recommendation.
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑ 3%	No specific recommendation
10 mg OD for 4 days	Fosamprenavir 1400 mg BID, 14 days	↓ 27%	No specific recommendation

[&] Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.
Increase is indicated as "↑", decrease as "↓"

OD = once daily; SD = single dose; BID = twice daily

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use appropriate contraceptive measures during treatment (see section 4.3).

Pregnancy
Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

ATOZET
ATOZET is contraindicated during pregnancy (see section 4.3). No clinical data are available on the use of ATOZET during pregnancy. ATOZET should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with ATOZET should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

The co-administration of ezetimibe and atorvastatin in pregnant rats indicated that there was a test article-related increase in the skeletal variation "reduced ossification of the sternebrae" in the high dose ezetimibe/atorvastatin group. This may be related to the observed decrease in foetal body weights. In pregnant rabbits a low incidence of skeletal deformities (fused sternebrae, fused caudal vertebrae and asymmetrical sternebrae variation) were observed.

Atorvastatin
Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown toxicity to reproduction (see section 5.3). Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis.

Ezetimibe
No clinical data are available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development (see section 5.3).

Breast-feeding
ATOZET is contraindicated during breast-feeding. Because of the potential for serious adverse reactions, women taking ATOZET should not breast-feed their infants. Studies on rats have shown that ezetimibe is secreted into breast milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk. It is not known if the active components of ATOZET are secreted into human breast milk. (See section 4.3.)

Fertility
No fertility studies were conducted with ATOZET.

Atorvastatin
In animal studies atorvastatin had no effect on male or female fertility.

Ezetimibe
Ezetimibe had no effect on the fertility of male or female rats.

4.7 Effects on ability to drive and use machines

ATOZET has negligible influence on the ability to drive and use machines. However, when driving vehicles or operating machines, it should be taken into account that dizziness has been reported.

4.8 Undesirable effects

Summary of the safety profile

ATOZET (or co-administration of ezetimibe and atorvastatin equivalent to ATOZET) has been evaluated for safety in more than 2,400 patients in 7 clinical trials.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of ATOZET (or co-administration of ezetimibe and atorvastatin equivalent to ATOZET) or ezetimibe or atorvastatin or reported from post-marketing use with ATOZET or ezetimibe or atorvastatin are listed in Table 3. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common ≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); and not known (cannot be estimated from the available data).

Table 3
Adverse Reactions

System organ class Frequency	**Adverse reaction**
Infections and infestations	
Uncommon	influenza
Not known	nasopharyngitis
Blood and lymphatic system disorders	
Not known	thrombocytopenia
Immune system disorders	
Not known	hypersensitivity, including anaphylaxis, angioedema, rash, and urticaria
Metabolism and nutrition disorders	
Not known	decreased appetite; anorexia; hyperglycaemia; hypoglycaemia
Psychiatric disorders	
Uncommon	depression; insomnia; sleep disorder
Not known	nightmares
Nervous system disorders	
Uncommon	dizziness; dysgeusia; headache; paraesthesia
Not known	hypoesthesia; amnesia; peripheral neuropathy; myasthenia gravis
Eye disorders	
Not known	vision blurred; visual disturbance; ocular myasthenia
Ear and labyrinth disorders	
Not known	tinnitus; hearing loss
Cardiac disorders	
Uncommon	sinus bradycardia
Vascular disorders	
Uncommon	hot flush
Not known	hypertension
Respiratory, thoracic and mediastinal disorders	
Uncommon	dyspnoea
Not known	cough; pharyngolaryngeal pain; epistaxis
Gastrointestinal disorders	
Common	diarrhoea
Uncommon	abdominal discomfort; abdominal distension; abdominal pain; abdominal pain lower; abdominal pain upper; constipation; dyspepsia; flatulence; frequent bowel movements; gastritis; nausea; stomach discomfort
Not known	pancreatitis; gastro-oesophageal reflux disease; eructation; vomiting; dry mouth
Hepatobiliary disorders	
Not known	hepatitis; cholelithiasis; cholecystitis; cholestasis; fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	
Uncommon	acne; urticaria
Not known	alopecia; skin rash; pruritus; erythema multiforme; angioneurotic oedema; dermatitis bullous including erythema multiforme,

	Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Common	myalgia
Uncommon	arthralgia; back pain; muscle fatigue; muscle spasms; muscular weakness; pain in extremity
Not known	myopathy/rhabdomyolysis; muscle rupture; tendinopathy, sometimes complicated by rupture; neck pain; joint swelling; myositis; lupus-like syndrome; immune-mediated necrotizing myopathy (see section 4.4)
Reproductive system and breast disorders	
Not known	gynaecomastia
General disorders and administration site conditions	
Uncommon	asthenia; fatigue; malaise; oedema
Not known	chest pain; pain; peripheral oedema; pyrexia
Investigations	
Uncommon	ALT and/or AST increased; alkaline phosphatase increased; blood creatine phosphokinase (CPK) increased; gamma-glutamyltransferase increased; hepatic enzyme increased; liver function test abnormal; weight increased
Not known	white blood cells urine positive

Laboratory Values
In controlled clinical trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥3 X ULN, consecutive) was 0.6% for patients treated with ATOZET. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline spontaneously or after discontinuation of therapy (see section 4.4).

The following adverse events have been reported with some statins:

- sexual dysfunction
- exceptional cases of interstitial lung disease, especially with long-term therapy (see section 4.4)
- diabetes mellitus: frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI> 30 kg/m^2, raised triglycerides, history of hypertension)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

ATOZET
In the event of an overdose, symptomatic and supportive measures should be employed. Liver function tests should be performed and serum CPK levels should be monitored.

Ezetimibe
In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hyperlipidaemia for up to 56 days, was generally well tolerated. A few cases of overdose have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In animals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

Atorvastatin
Due to extensive atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA reductase inhibitors in combination with other lipid modifying agents, ATC code: C10BA05

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.

Mechanism of action

ATOZET

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. ATOZET contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. ATOZET reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol absorption and synthesis.

Ezetimibe

Ezetimibe inhibits the intestinal absorption of cholesterol. Ezetimibe is orally active and 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 stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver; statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. 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, ethinyl estradiol, or fat soluble vitamins A and D.

Atorvastatin

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (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 receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medicinal products.

Atorvastatin has been shown to reduce concentrations of total-C (30% - 46%), LDL-C (41% - 61%), apolipoprotein B (34% - 50%), and triglycerides (14% - 33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Clinical efficacy and safety

In controlled clinical studies, ATOZET significantly reduced total-C, LDL-C, Apo B, and TG, and increased HDL-C in patients with hypercholesterolaemia.

Primary Hypercholesterolaemia

In a placebo-controlled study, 628 patients with hyperlipidaemia 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) for up to 12-weeks.

Patients receiving all doses of ATOZET were compared to those receiving all doses of atorvastatin. ATOZET lowered total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone. (See Table 4.)

Table 4
Response to ATOZET in Patients with Primary Hyperlipidaemia
(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 medicinal product
[c] ATOZET pooled (10/10-10/80 mg) 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).

In a controlled study, the Titration of Atorvastatin Versus Ezetimibe Add-On to Atorvastatin in Patients with Hypercholesterolaemia (TEMPO) study, 184 patients, with an LDL-C level ≥2.6 mmol/L and ≤4.1 mmol/L and at moderate high risk for CHD, received atorvastatin 20 mg for a minimum of 4 weeks prior to randomisation. Patients not at an LDL-C level <2.6 mmol/L were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ATOZET 10/20) or atorvastatin 40 mg for 6 weeks.

ATOZET 10/20 was significantly more effective than doubling the dose of atorvastatin to 40 mg in further reducing total-C (-20% vs. -7%), LDL-C (-31% vs. -11%), Apo B (-21% vs. -8%), and non-HDL-C (-27% vs. -10%). Results for HDL-C and TG between the two treatment groups were not significantly different. Also, significantly more patients receiving ATOZET 10/20 attained LDL-C <2.6 mmol/L compared to those receiving atorvastatin 40 mg, 84% vs. 49%.

In a controlled study, The Ezetimibe Plus Atorvastatin Versus Atorvastatin Titration in Achieving Lower LDL-C Targets in Hypercholesterolaemic Patients (EZ-PATH) study, 556 high-cardiovascular-risk patients with a LDL-C level ≥1.8 mmol/L and ≤4.1 mmol/L received atorvastatin 40 mg for a minimum of 4 weeks prior to randomisation. Patients not at a LDL-C level <1.8 mmol/L were randomised to receive either co-administered ezetimibe and atorvastatin (equivalent to ATOZET 10/40) or atorvastatin 80 mg for 6 weeks.

ATOZET 10/40 was significantly more effective than doubling the dose of atorvastatin to 80 mg in further reducing total-C (-17% vs. -7%), LDL-C (-27% vs. -11%), Apo B (-18% vs. -8%), TG (-12% vs. -6%), and non-HDL-C (-23% vs. -9%). Results for HDL-C between the two treatment groups were not significantly different. Also, significantly more patients receiving ATOZET 10/40 attained LDL-C <1.8 mmol/L compared to those receiving atorvastatin 80 mg, 74% vs. 32%.

In a placebo-controlled, 8-week study, 308 hypercholesterolaemic patients receiving atorvastatin and not at National Cholesterol Education Program (NCEP) LDL-C goal (LDL-C goal based upon baseline LDL-C and CHD risk status) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going atorvastatin therapy.

Among patients not at LDL-C goal at baseline (~83%), significantly more patients receiving ezetimibe co-administered with atorvastatin achieved their LDL-C goal compared to patients receiving placebo co-administered with atorvastatin, 67% vs. 19%. Ezetimibe added to atorvastatin therapy lowered LDL-C significantly more than placebo added to atorvastatin therapy, 25% vs. 4%. Ezetimibe added to atorvastatin therapy also significantly decreased total-C, Apo B, and TG compared with placebo added to atorvastatin therapy.

In a controlled, 12-week, 2-phase study, 1539 high-cardiovascular-risk patients, with a LDL-C level between 2.6 and 4.1 mmol/L, on atorvastatin 10 mg daily were randomised to receive: atorvastatin 20 mg, rosuvastatin 10 mg, or ATOZET 10/10. After 6 weeks of treatment (Phase I), patients taking atorvastatin 20 mg who failed to achieve a LDL-C level <2.6 mmol/L were switched to either atorvastatin 40 mg or ATOZET 10/20 for 6 weeks (Phase II), and similar patients taking rosuvastatin 10 mg during Phase I were switched to either rosuvastatin 20 mg or ATOZET 10/20. 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* in High-Risk Patients with a LDL-C Level Between 2.6 and 4.1 mmol/L 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§
Rosuvastatin 10 mg	939	-7.7§	-13.0§	-6.9#	-1.1	+1.1	-10.6§
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	-3.8Þ	-6.9Þ	-5.4	-3.1	+1.7	-5.8Þ
Switched from rosuvastatin 10 mg							
ATOZET 10/20	231	-11.8	-17.1	-11.9	-10.2	+0.1	-16.2
Rosuvastatin 20 mg	205	-4.5Þ	-7.5Þ	-4.1Þ	-3.2ß	+0.8	-6.4Þ

* Co-administered ezetimibe and atorvastatin equivalent to ATOZET 10/10 or ATOZET 10/20
† 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
# p<0.05 versus ATOZET 10/10
Þ p<0.001 versus ATOZET 10/20
ß p<0.05 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 or rosuvastatin 20 mg.

In a placebo-controlled study, the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, patients with an acute coronary syndrome (non Q-wave MI or unstable angina) were randomised to receive atorvastatin 80 mg/day (n=1538) or placebo (n=1548). Treatment was initiated during the acute phase after hospital admission and lasted for 16 weeks. Atorvastatin 80 mg/day provided a 16% (p=0.048) reduction in risk of the combined primary endpoint: death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalisation. This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018).

ATOZET contains atorvastatin. In a placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin 10 mg on fatal and non-fatal CHD was assessed in 10,305 hypertensive patients, 40-80 years old, with TC levels ≤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<0.001) reduced the relative risk for: fatal CHD plus nonfatal MI by 36%

(absolute risk reduction = 1.1%); total cardiovascular events and revascularisation procedures by 20% (absolute risk reduction = 1.9%); and total coronary events by 29% (absolute risk reduction = 1.4%).

In a placebo-controlled study, the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin 10 mg on cardiovascular disease (CVD) endpoints was assessed in 2838 patients, 40-75 years old, with type 2 diabetes, one or more cardiovascular risk factors, LDL ≤4.1 mmol/L, and TG ≤6.8 mmol/L. Patients were followed for a median duration of 3.9 years. Atorvastatin 10 mg significantly ($p<0.05$) reduced: the rate of major cardiovascular events by 37% (absolute risk reduction = 3.2%); the risk of stroke by 48% (absolute risk reduction = 1.3%); and the risk of MI by 42% (absolute risk reduction = 1.9%).

Prevention of Cardiovascular Events
In an ezetimibe/simvastatin, multicentre, randomised, double-blind, active-control study, 18,144 patients enrolled within 10 days of hospitalisation for acute coronary syndrome (ACS; either acute myocardial infarction [MI] or unstable angina [UA]). All patients were randomised in a 1:1 ratio to receive either ezetimibe/simvastatin 10/40 mg (n=9067) or simvastatin 40 mg (n=9077) and followed for a median of 6.0 years.

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

The primary endpoint was a composite consisting of cardiovascular death, major coronary events (MCE; defined as non-fatal myocardial infarction, documented unstable angina that required hospitalisation, or any coronary revascularisation procedure occurring at least 30 days after randomised treatment assignment) and non-fatal stroke. The study demonstrated that treatment with ezetimibe/simvastatin provided incremental benefit in reducing the primary composite endpoint of cardiovascular death, MCE, and non-fatal stroke compared with simvastatin alone (relative risk reduction of 6.4%, p=0.016). The primary endpoint occurred in 2572 of 9067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2742 of 9077 patients (7-year KM rate 34.67%) in the simvastatin alone group. (See Figure 1 and Table 6.) This incremental benefit is expected to be similar with co-administration of ezetimibe and atorvastatin. Total mortality was unchanged in this high risk group.

There was an overall benefit for all strokes; however there was a small non-significant increase in haemorrhagic stroke in the ezetimibe-simvastatin group compared with simvastatin alone. The risk of haemorrhagic stroke for ezetimibe co-administered with higher potency statins in long-term outcome studies has not been evaluated.

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

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

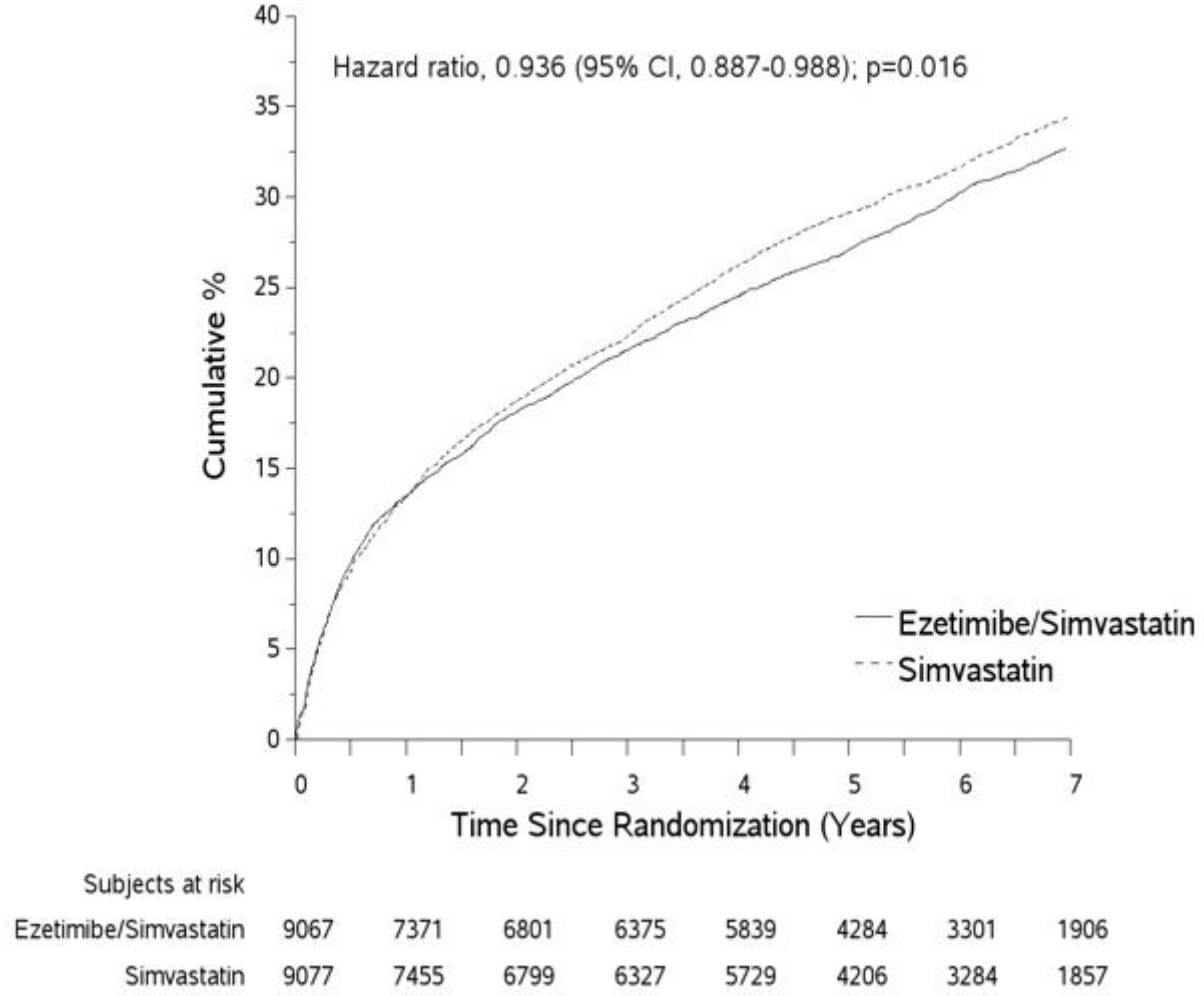


Table 6
Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	**Ezetimibe/Simvastatin 10/40 mg* (N=9067)**		**Simvastatin 40 mg† (N=9077)**		**Hazard Ratio (95% CI)**	**p-value**
	n	K-M %‡	n	K-M %‡		
Primary Composite Efficacy Endpoint						
(CV death, Major Coronary Events and non-fatal stroke)	2572	32.72%	2742	34.67%	0.936 (0.887, 0.988)	0.016
Components of Primary Composite Endpoint and Select Efficacy Endpoints (first occurrences of specified event at any time)						
Cardiovascular death	537	6.89%	538	6.84%	1.000 (0.887, 1.127)	0.997
Major Coronary Event:						
Non-fatal MI	945	12.77%	1083	14.41%	0.871 (0.798, 0.950)	0.002
Unstable angina requiring hospitalisation	156	2.06%	148	1.92%	1.059 (0.846, 1.326)	0.618
Coronary revascularisation after 30 days	1690	21.84%	1793	23.36%	0.947 (0.886, 1.012)	0.107
Non-fatal stroke	245	3.49%	305	4.24%	0.802 (0.678, 0.949)	0.010

* 6% were uptitrated to ezetimibe/simvastatin 10/80 mg.
† 27% were uptitrated to simvastatin 80 mg.
‡ Kaplan-Meier estimate at 7 years.

Homozygous Familial Hypercholesterolaemia (HoFH)
A double-blind, randomised, 12-week study was performed in patients with a clinical and/or genotypic diagnosis of HoFH. Data were analysed from a subgroup of patients (n=36) receiving atorvastatin 40 mg at baseline. 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, 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. Following at least 4 weeks of treatment, the atorvastatin dose could be doubled to a maximum dose of 80 mg. At the end of the 24 months, ATOZET (10/40 and 10/80 pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week study.
The European Medicines Agency has waived the obligation to submit the results of studies with ATOZET in all subsets of the paediatric population in the treatments of hypercholesterolaemia and mixed hyperlipidaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

ATOZET
ATOZET has been shown to be bioequivalent to co-administration of corresponding doses of ezetimibe and atorvastatin tablets.

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

Concomitant food administration (high-fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe when administered as 10-mg tablets.

Atorvastatin
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

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

Atorvastatin
Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥98% bound to plasma proteins.

Biotransformation
Ezetimibe
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.

Atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. *In vitro*, inhibition of

HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

Ezetimibe

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

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product does not appear to undergo significant 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 approximately 20 to 30 hours due to the contribution of active metabolites.

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin.

Paediatric population

Ezetimibe

The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

Atorvastatin

In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage 2 (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolaemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Elderly

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 are comparable between elderly and younger subjects treated with ezetimibe.

Atorvastatin

Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Hepatic impairment

Ezetimibe

After a single 10-mg dose of ezetimibe, the mean 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 dose 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 sections 4.2 and 4.4).

Atorvastatin

Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

Renal impairment

Ezetimibe

After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73 m ^{2}), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9).

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

Atorvastatin

Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Gender

Ezetimibe

Plasma concentrations for total ezetimibe are slightly higher (approximately 20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe.

Atorvastatin

Concentrations of atorvastatin and its active metabolites in women differ from those in men (women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

SLCO1B1 polymorphism

Atorvastatin

Hepatic uptake of all HMG-CoA reductase inhibitors, including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data

ATOZET

In three-month co-administration studies in rats and dogs with ezetimibe and atorvastatin, the toxic effects observed were essentially those typically associated with statins. The statin-like histopathologic findings were limited to the liver. Some of the toxic effects were more pronounced than those observed during treatment with statins alone. This is attributed to pharmacokinetic and/or pharmacodynamic interactions following co-administration.

The co-administration of ezetimibe and atorvastatin in pregnant rats indicated that there was a test article-related increase in the skeletal variation "reduced ossification of the sternebrae" in the high dose (1000/108.6 mg/kg) ezetimibe/atorvastatin group. This may be related to the observed decrease in foetal body weights. In pregnant rabbits a low incidence of skeletal deformities (fused sternebrae, fused caudal vertebrae and asymmetrical sternebrae variation) were observed.

In a series of *in vivo* and *in vitro* assays, ezetimibe, given alone or co-administered with atorvastatin, exhibited no genotoxic potential.

Ezetimibe

Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effects. In dogs treated for four weeks with ezetimibe (≥0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one-year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out.

Long-term carcinogenicity tests on ezetimibe were negative.

Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day.

Atorvastatin
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 *in vitro* tests and 1 *in vivo* assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits, and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Ezetimibe Layer
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Cellulose, microcrystalline
Povidone
Sodium laurilsulfate

Atorvastatin Layer
Cellulose, microcrystalline
Lactose monohydrate
Hydroxypropylcellulose
Croscarmellose sodium
Polysorbate 80
Calcium carbonate
Magnesium stearate
Silica, colloidal anhydrous

Film coating
Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from oxygen.

6.5 Nature and contents of container

Packs of 10, 30, 90, and 100 film-coated tablets in nitrogen-purged aluminium/aluminium (oPA-Al-PVC cavity with Al lidding) blisters.

Packs of 30 x 1 and 45 x 1 film-coated tablets in unit dose nitrogen-purged aluminium/aluminium (oPA-Al-PVC cavity with Al lidding) blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Organon Pharma (Ireland) Limited
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