SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ezetimibe/Atorvastatin 10 mg/40 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg of ezetimibe and 40 mg of atorvastatin (as atorvastatin calcium trihydrate).

Excipient(s) with known effect

Each film-coated tablet contains 283.39 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White and light pink oval-shaped, biconvex film-coated tablets, debossed with “40” on one side and plain on the other, size approx. 17 mm (length) x 6 mm (width).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Cardiovascular Events

Ezetimibe/Atorvastatin Tablets is indicated as substitution therapy in adult patients who are adequately controlled with atorvastatin and ezetimibe given concurrently, at the same dose level as in the fixed dose combination, but as separate products to reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) (see section 5.1).

Hypercholesterolaemia

Ezetimibe/Atorvastatin Tablets is indicated as adjunct to diet for treatment of primary (heterozygous and homozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia in adult patients who are adequately controlled with atorvastatin and ezetimibe given concurrently at the same dose level as in the fixed combination, but as separate products.

4.2 Posology and method of administration

Posology

The dose range of Ezetimibe/Atorvastatin Tablets is 10/10 mg/day through 10/80 mg/day.

The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezetimibe/Atorvastatin Tablets.

Ezetimibe/Atorvastatin Tablets is not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the mono-components and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Co-administration with other medicines

Dosing of Ezetimibe/Atorvastatin Tablets 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 or letermovir for cytomegalovirus prophylaxis infection concomitantly with Ezetimibe/Atorvastatin Tablets, the dose of Ezetimibe/Atorvastatin Tablets should not exceed 10/20 mg/day (see sections 4.4 and 4.5).

The use of ezetimibe/atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin (see sections 4.4. and 4.5).

Elderly

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

Hepatic impairment

Ezetimibe/Atorvastatin Tablets should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Ezetimibe/Atorvastatin Tablets 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).

Paediatric population

The safety and efficacy of Ezetimibe/Atorvastatin Tablets in children has not been established (see section 5.2). No data are available.

Method of administration

Ezetimibe/Atorvastatin Tablets is for oral administration. Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

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

Ezetimibe/Atorvastatin Tablets 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.

Ezetimibe/Atorvastatin Tablets 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.

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

Before the treatment

Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets.
- If such symptoms occur whilst a patient is receiving treatment with Ezetimibe/Atorvastatin Tablets, 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 Ezetimibe/Atorvastatin Tablets or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.
- Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets, the risk of rhabdomyolysis is increased when Ezetimibe/Atorvastatin Tablets 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, letermovir, 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, ledipasvir/sofosbuvir), 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 Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Daptomycin

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors (e.g. atorvastatin) and daptomycin (see section 4.5). Consideration should be given to temporarily suspend Ezetimibe/Atorvastatin Tablets in patients taking daptomycin unless the benefits of concomitant administration outweigh the risk. If co-administration cannot be avoided, CK levels should be measured 2-3 times per week and patients should be closely monitored for any signs or symptoms that might represent myopathy.

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 Ezetimibe/Atorvastatin Tablets is recommended.

Ezetimibe/Atorvastatin Tablets 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, Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets and fibrates is not recommended (see section 4.5).

Ciclosporin

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

Anticoagulants

If Ezetimibe/Atorvastatin Tablets 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

Ezetimibe/Atorvastatin Tablets contains lactose (as lactose monohydrate). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).

Pharmacokinetic interactions

Ezetimibe/Atorvastatin Tablets

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

Effects of other medicinal products on Ezetimibe/Atorvastatin Tablets

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 Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets cannot be avoided, lower starting and maximum doses of Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets 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 can increase the systemic exposure of atorvastatin. Ciclosporin and letermovir are both inhibitors of transporters involved in the disposition of atorvastatin, i.e. OATP1B1/1B3, P-gp, and BCRP leading to an increased 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 Ezetimibe/Atorvastatin Tablets and clinical monitoring for efficacy is recommended (see Table 1).

The use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4).

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: Cases of myopathy and/or rhabdomyolysis have been reported with HMG-CoA reductase inhibitors (e.g. atorvastatin) co-administered with daptomycin. If coadministration cannot be avoided, appropriate clinical monitoring is recommended (see section 4.4).

Boceprevir: Exposure to atorvastatin was increased when administered with boceprevir. When co-administration with Ezetimibe/Atorvastatin Tablets is required, starting with the lowest possible dose of Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin , the dose of Ezetimibe/Atorvastatin Tablets should not exceed a daily dose of 10/20 mg during co-administration with boceprevir.

Effects of Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets 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 oestradiol.

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 Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets 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**		
	Dose (mg)	**Ratio of AUC[&]**	**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	In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.
Telaprevir 750 mg q8h, 10 days	20 mg, SD	7.9	
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	8.7	
Lopinavir 400 mg BID / Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	5.9	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	4.5	
Saquinavir 400 mg BID / Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	3.9	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Clinical Recommendation[#]
Darunavir 300 mg BID / Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	3.4	recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Itraconazole 200 mg OD, 4 days	40 mg SD	3.3	
Fosamprenavir 700 mg BID / Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	2.5	
Fosamprenavir 1,400 mg BID, 14 days	10 mg OD for 4 days	2.3	
Letermovir 480 mg OD, 10 days	20 mg SD	3.29	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing letermovir.
Nelfinavir 1,250 mg BID, 14 days	10 mg OD for 28 days	1.74	No specific recommendation
Elbasvir 50 mg OD / Grazoprevir 200 mg OD, 13 days	10 mg SD	1.95	The dose of atorvastatin should not exceed a daily dose of 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	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Grapefruit juice, 240 ml OD *	40 mg, SD	1.37	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	1.51	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	1.33	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single dose	80 mg, SD	1.18	No specific recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 2 weeks	1.00	No specific recommendation.
Colestipol 10 g BID, 24 weeks	40 mg OD for 8 weeks	0.74**	No specific recommendation.

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Clinical Recommendation[#]
Antacid suspension of magnesium and aluminium hydroxides, 30 ml QID, 17 days	10 mg OD for 15 days	0.66	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	0.59	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	1.12	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	0.20	
Gemfibrozil 600 mg BID, 7 days	40 mg SD	1.35	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40 mg SD	1.03	Lower starting dose and clinical monitoring of these patients is recommended.
Boceprevir 800 mg TID, 7 days	40 mg SD	2.3	Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir.

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

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) HMG-CoA reductase inhibitors 1.3 fold.

** Ratio based on a single sample taken 8-16 h post dose.

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		
	Medicinal product/Dose (mg)	Ratio of AUC[&]	Clinical Recommendation

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	**Ratio of AUC[&]**	**Clinical Recommendation**
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	1.15	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months • norethindrone 1 mg • ethinyl estradiol 35 µg	 1.28 1.19	No specific recommendation.
80 mg OD for 15 days	*Phenazone, 600 mg SD	1.03	No specific recommendation.
10 mg, SD	Tipranavir 500 mg BID /ritonavir 200 mg BID, 7 days	1.08	No specific recommendation.
10 mg, OD for 4 days	Fosamprenavir 1,400 mg BID, 14 days	0.73	No specific recommendation.
10 mg OD for 4 days	Fosamprenavir 700 mg BID / ritonavir 100 mg BID, 14 days	0.99	No specific recommendation.

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

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.

Ezetimibe/Atorvastatin Tablets

Ezetimibe/Atorvastatin Tablets is contraindicated during pregnancy (see section 4.3). No clinical data are available on the use of Ezetimibe/Atorvastatin Tablets during pregnancy. Ezetimibe/Atorvastatin Tablets should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant.

Treatment with Ezetimibe/Atorvastatin Tablets 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

Ezetimibe/Atorvastatin Tablets is contraindicated during breast-feeding. Because of the potential for serious adverse reactions, women taking Ezetimibe/Atorvastatin Tablets 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 Ezetimibe/Atorvastatin Tablets are secreted into human breast milk. (See section 4.3.)

Fertility

No fertility studies were conducted with Ezetimibe/Atorvastatin Tablets.

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

Ezetimibe/Atorvastatin Tablets 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

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of Ezetimibe/Atorvastatin Tablets (or co-administration of ezetimibe and atorvastatin equivalent to Ezetimibe/Atorvastatin Tablets) or ezetimibe or atorvastatin or reported from post-marketing use with Ezetimibe/Atorvastatin Tablets or ezetimibe or atorvastatin are listed in Table below. 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).

System Organ Class	**Undesirable Effect**	**Frequency**		
		Atorvastatin	**Ezetimibe**	**Ezetimibe + Statin**
Infections and infestations	Nasopharyngitis	Common	-	Not known
	Influenza	-		Uncommon
Blood and lymphatic disorders	Thrombocytopenia	Rare	Not known	Not known
Immune system disorder	Allergic reactions	Common	-	-
	Anaphylactic reactions	Very rare	-	-
	Hypersensitivity, including rash, urticarial, anaphylaxis and angioedema	-	Not known	Not known
Metabolism and nutrition disorders	Hyperglycaemia	Common	-	Not known
	Hypoglycaemia, weight gain, anorexia	Uncommon	-	Not known
	Decreased appetite	-	Uncommon	Not known
Psychiatric disorders	Nightmare	Uncommon	-	Not known
	Insomnia	Uncommon	-	Uncommon
	Depression	-	Not known	Uncommon
	Sleep disorder	-		Uncommon
Nervous system disorder	Headache	Common	Common	Uncommon
	Dizziness	Uncommon	Not known	Uncommon
	Dysgeusia,	Uncommon	-	Uncommon
	Amnesia	Uncommon	-	Not known
	Hypoesthesia	Uncommon	-	Not known
	Paraesthesia	Uncommon	Uncommon	Uncommon
	Peripheral neuropathy	Rare	-	Not known
	Myasthenia gravis	Not known	-	Not known

System Organ Class	Undesirable Effect	Frequency		
		Atorvastatin	Ezetimibe	Ezetimibe + Statin
Eye disorders	Vision blurred	Uncommon	-	Not known
	Visual disturbance	Rare	-	Not known
	Ocular myasthenia	-Not known	-	Not known
Ear and labyrinth disorders	Tinnitus	Uncommon	-	Not known
	Hearing loss	Very rare	-	Not known
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis	Common	-	Not known
	Cough	-	Uncommon	Not known
	Dyspnoea	-	Not known	Uncommon
Gastrointestinal disorders	Flatulence	Common	Common	Uncommon
	Diarrhoea	Common	Common	Common
	Constipation	Common	Not known	Uncommon
	Nausea	Common	Uncommon	Uncommon
	Dyspepsia	Common	Uncommon	Uncommon
	Vomiting, eructation	Uncommon	-	Not known
	Pancreatitis	Uncommon	Not known	Not known
	Abdominal pain	Uncommon	Common	Uncommon
	Gastrooesophageal reflux disease	-	Uncommon	Not known
	Dry mouth	-	Uncommon	Not known
	Gastritis	-	Uncommon	Uncommon
	Abdominal discomfort, abdominal distension, abdominal pain lower, abdominal pain upper, frequent bowel movements, stomach discomfort	-	-	Uncommon
Hepatobiliary disorders	Hepatitis	Uncommon	Not known	Not known
	Cholestasis	Rare	-	Not known
	Hepatic failure	Very rare	-	Not known
	Cholelithiasis, cholecystitis	-	Not known	Not known
Skin and subcutaneous tissue disorders	Urticaria	Uncommon	Uncommon	Uncommon
	Skin rash, pruritus	Uncommon	Uncommon	Not known
	Alopecia	Uncommon	-	Not known
	Angioneurotic oedema, dermatitis bullous including Stevens-Johnson syndrome and toxic epidermal necrolysis	Rare	-	Not known
	Erythema multiforme	Rare	Not known	Not known
	Acne	-	-	Uncommon
	Lichenoid drug reaction	Rare	-	Not known
Musculoskeletal and connective	Arthralgia, muscle spasms	Common	Uncommon	Uncommon
	Joint swelling	Common	-	Not known
	Pain in extremity, back pain	Common	Uncommon	Uncommon

System Organ Class	Undesirable Effect	Frequency		
		Atorvastatin	Ezetimibe	Ezetimibe + Statin
tissue disorders	Muscle fatigue	Uncommon	-	Uncommon
	Muscular weakness	-	Uncommon	Uncommon
	Neck pain	Uncommon	Uncommon	Not known
	Myalgia	Common	Common	Common
	Myositis, tendinopathy (sometimes complicated by rupture)	Rare	-	Not known
	Immune-mediated necrotising myopathy	Not known	-	Not known
	Myopathy/rhabdomyolysis	Rare	Not known	Not known
	Muscle rupture	Rare		Not known
	Lupus-like syndrome	Very rare	-	Not known
Reproductive system and breast disorders	Gynecomastia	Very rare	-	Not known
Cardiac disorders	Sinus bradycardia	-	-	Uncommon
Vascular disorders	Hot flush	-	Uncommon	Uncommon
	Hypertension	-	Uncommon	Not known
	Vasculitis	Rare	-	Not known
General disorders and administration site conditions	Oedema peripheral	Uncommon	Uncommon	Not known
	Asthenia	Uncommon	Uncommon	Uncommon
	Chest pain	Uncommon	Uncommon	Not known
	Fatigue	Uncommon	Common	Uncommon
	Malaise	Uncommon	-	Uncommon
	Pyrexia	Uncommon	-	Not known
	Pain	-	Uncommon	Not known
	Oedema	-	-	Uncommon
Investigations	Liver function test abnormal, blood creatine kinase increased	Common	-	-
	White blood cells urine positive	Uncommon	-	Not known
	ALT and/or AST increased	-	Common	Uncommon
	Blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal	-	Uncommon	Uncommon
	Hepatic enzyme increased, weight increased	-	-	Uncommon
	Alkaline phosphatase increased	-	-	Uncommon

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 Ezetimibe/Atorvastatin Tablets. 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/ m2, 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Ezetimibe/Atorvastatin Tablets

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, Combinations of various lipid modifying agents, ATC code: C10BA05

Ezetimibe/Atorvastatin Tablets 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

Ezetimibe/Atorvastatin Tablets

Plasma cholesterol is derived from intestinal absorption and endogenous synthesis. Ezetimibe/Atorvastatin Tablets contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe/Atorvastatin Tablets 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

Primary Hypercholesterolaemia

In a multicentre, double-blind, placebo-controlled study a total of 148 men and women with primary hypercholesterolaemia and coronary heart disease (CHD) were randomised to receive treatment for 6 weeks with either ezetimibe (EZE) 10 mg + atorvastatin (ATV) 10 mg (EZE + ATV; n = 72) or placebo/atorvastatin 10 mg (ATV; n = 76). The primary efficacy variable was the mean percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline to study endpoint. At 6 weeks, EZE + ATV provided a significantly greater adjusted mean change from baseline in LDL-C compared with ATV monotherapy (-50.5 % vs. -36.5 %; $p < 0.0001$), equating to an additional 14.1% reduction (95% Cl -17.90, -10.19) in LDL-C. A significantly higher proportion of patients on EZE + ATV achieved the new Joint British Societies (JBS 2) recommended LDL-C goal of < 2 mmol/l (62 % vs. 12 % with ATV alone; $p < 0.0001$) and the JBS 2 minimum treatment standard of < 3 mmol/l (93 % vs. 79 % with ATV alone). Patients receiving EZE+ATV were 12 times more likely to reach LDL-C targets (odds ratio 12.1; 95 % Cl 5.8, 25.1; $p < 0.0001$) compared with patients receiving ATV monotherapy.

In a meta-analysis of combination therapy of ezetimibe and atorvastatin and atorvastatin monotherapy 11 randomised, parallel-group trials with 5,206 participants were analysed. Four doses of the comparisons were also included: the combination therapy of Ezetimibe (10 mg) and Atorvastatin (10 mg) (E10 + A10) versus

Atorvastatin (20 mg) monotherapy (A20); E10 + A10 vs. A10; E10 + A20 vs. A40; E10 + A40 vs. A80. Compared with Atorvastatin monotherapy, the overall efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C (MD = − 15.38, 95 % CI: -16.17 to − 14.60; I2 = 26.2 %, n = 17), TC (MD = − 9.51, 95 % CI: -10.28 to − 8.74; I2 = 33.7 %, n = 17) and TG (MD = − 6.42, 95 % CI: -7.78 to − 5.06; I2 = 0 %, n = 15) and raising HDL-C (MD = 0.95, 95 % CI: 0.34 to 1.57; I2 = 0 %, n = 17) was significant. The efficacy of the comparison on HDL-C was largely significant for the different doses. The overall efficacy and subgroup's efficacy of combination therapy of Ezetimibe and Atorvastatin on lowering LDL-C, TC and TG was significantly better than Atorvastatin monotherapy. The overall and the E10 + A10/A20 group's effectiveness of combination therapy on raising HDL-C were significantly.

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 = 9,067) or simvastatin 40 mg (n = 9,077) and followed for a median of 6.0 years.

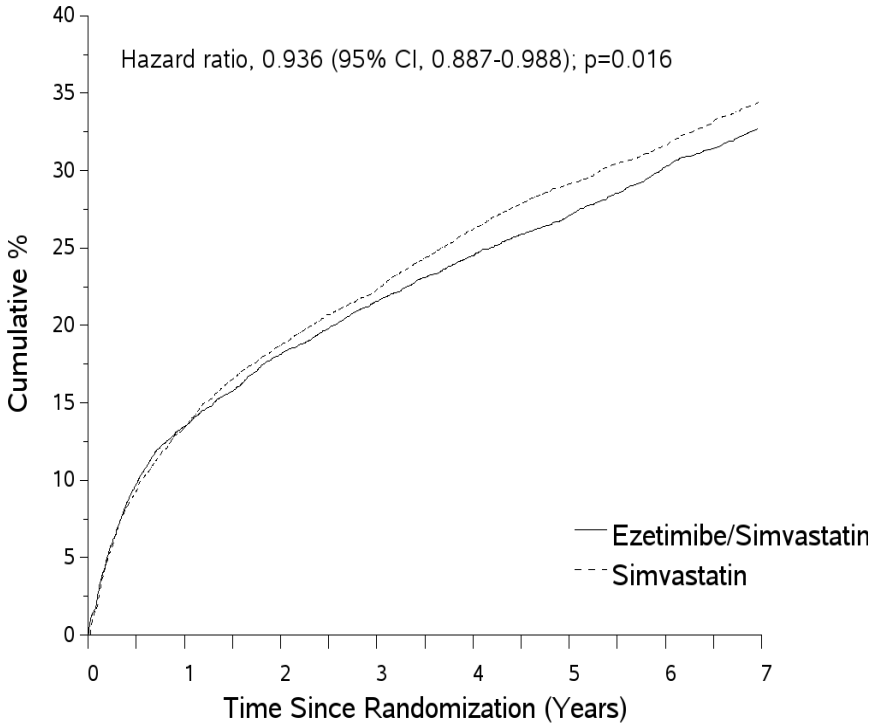
Patients had a mean age of 63.6 years; 76% were male, 84% were Caucasian, and 27% were diabetic. The average LDL-C value at the time of study qualifying event was 80 mg/dL (2.1 mmol/L) for those on lipid-lowering therapy (n = 6,390) and 101 mg/dL (2.6 mmol/L) for those not on previous lipid-lowering therapy (n = 11,594). 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 2,572 of 9,067 patients (7-year Kaplan-Meier [KM] rate 32.72%) in the ezetimibe/simvastatin group and 2,742 of 9,077 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



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

Table 3 Major Cardiovascular Events by Treatment Group in All Randomised Patients in IMPROVE-IT

Outcome	Ezetimibe/Simvastatin 10/40 mg* (N=9,067)		Simvastatin 40 mg† (N=9,077)		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)	2,572	32.72%	2,742	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%	1,083	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	1,690	21.84%	1,793	1,793	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 (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 (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 (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, the combination of ezetimibe with atorvastatin (10/40 and 10/80 pooled) produced a reduction of LDL-C that was consistent with that seen in the 12-week study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ezetimibe/atorvastatin in all subsets of the paediatric population in the treatment of hypercholesterolaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Ezetimibe/Atorvastatin Tablets has been shown to be bioequivalent to co-administration of corresponding doses of ezetimibe and atorvastatin tablets.

Absorption

Ezetimibe

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (Cmax) 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 (Cmax) 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 P-glycoprotein (P-gp) 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 Cmax 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 m2), 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 Cmax 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

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 AUC_{0-24h} 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.

Ezetimibe and statin coadministered

In co-administration studies with ezetimibe and statins (including atorvastatin) the toxic effects observed were essentially those typically associated with statins. Some of the toxic effects were more pronounced than observed during treatment with statins alone. This is attributed to pharmacokinetic and pharmacodynamic interactions in co-administration therapy. No such interactions occurred in the clinical studies. Myopathies occurred in rats only after exposure to doses that were several times higher than the human therapeutic dose (approximately 20 times the AUC level for statins and 500 to 2,000 times the AUC level for the active metabolites). In a series of in vivo and in vitro assays ezetimibe co-administered with statins exhibited no genotoxic potential. The co-administration of ezetimibe and statins was not teratogenic in rats. In pregnant rabbits a small number of skeletal deformities (fused thoracic and caudal vertebrae, reduced number of caudal vertebrae) were observed. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Ezetimibe Layer

Lactose Monohydrate

Cellulose, Microcrystalline

Croscarmellose sodium

Iron Oxide red (E172)

Sodium Laurilsulfate

Povidone K30

Magnesium Stearate

Atorvastatin Layer

Cellulose, Microcrystalline

Croscarmellose Sodium

Lactose Monohydrate

Calcium Carbonate

Povidone K30

Polysorbate 80

Magnesium Stearate

Film coating

Opadry White containing Hypromellose 2910 (E464), Titanium Dioxide (E171), Talc (E553b), Propylene Glycol (E1520)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

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

6.5 Nature and contents of container

Packs of 30 film coated tablets in cold formed blister (OPA/Alu/PVC-Alu).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 49578/0049

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2026

10 DATE OF REVISION OF THE TEXT

13/02/2026