SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ezetimibe/Atorvastatine DOC 10 mg/10 mg harde capsules
Ezetimibe/Atorvastatine DOC 10 mg/20 mg harde capsules
Ezetimibe/Atorvastatine DOC 10 mg/40 mg harde capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ezetimibe/Atorvastatine DOC 10 mg/10 mg harde capsules
Each hard capsule contains 10 mg ezetimibe and 10 mg of atorvastatin (as atorvastatin calcium trihydrate).

Ezetimibe/Atorvastatine DOC 10 mg/20 mg harde capsules
Each hard capsule contains 10 mg ezetimibe and 20 mg of atorvastatin (as atorvastatin calcium trihydrate).

Ezetimibe/Atorvastatine DOC 10 mg/40 mg harde capsules
Each hard capsule contains 10 mg ezetimibe and 40 mg of atorvastatin (as atorvastatin calcium trihydrate).

Excipient with known effect
Each Ezetimibe/Atorvastatine DOC 10 mg/10 mg capsule contains 13 mg sucrose.
Each Ezetimibe/Atorvastatine DOC 10 mg/20 mg capsule contains 26 mg sucrose.
Each Ezetimibe/Atorvastatine DOC 10 mg/40 mg capsule contains 51.5 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules, hard

Ezetimibe/Atorvastatine DOC 10 mg/10 mg harde capsules:
Unmarked self-closing size 0, hard gelatin capsule with caramel coloured cap and yellow coloured body, filled with pellets and a tablet. The length of the capsule is about 21.7 mm.

Ezetimibe/Atorvastatine DOC 10 mg/20 mg harde capsules:
Unmarked self-closing size 0, hard gelatin capsule with reddish brown coloured cap and yellow coloured body, filled with pellets and a tablet. The length of the capsule is about 21.7 mm.

Ezetimibe/Atorvastatine DOC 10 mg/40 mg harde capsules:
Unmarked self-closing size 0, hard gelatin capsule with dark brown coloured cap and yellow coloured body, filled with pellets and a tablet. The length of the capsule is about 21.7 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ezetimibe/Atorvastatine DOC hard capsules are indicated as adjunct to diet as substitution therapy for treatment of adults with primary hypercholesterolemia, including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidaemia already controlled with the individual

substances given concurrently at the same dose level as in the fixed dose combination, but as separate products.

4.2 Posology and method of administration

Posology
Ezetimibe/Atorvastatine DOC is indicated in adult patients whose hypercholesterolemia is adequately controlled with separately administered monocomponent medicinal products of the same doses as the recommended combination.
The patient should be on an appropriate lipid-lowering diet and should continue on this diet during treatment with Ezetimibe/Atorvastatine DOC.

The recommended daily dose is one capsule of the given strength with or without food.
Ezetimibe/Atorvastatine DOC are not suitable for initial therapy. Treatment initiation or dose adjustment if necessary should only be done with the monocomponents and after setting the appropriate doses the switch to the fixed dose combination of the appropriate strength is possible.

Coadministration with bile acid sequestrants
Ezetimibe/Atorvastatine DOC should be taken either ≥2 hours before or ≥4 hours after administration of a bile acid sequestrant.

Co-administration with other medicines
In patients taking the hepatitis C antiviral agents elbasvir/grazoprevir or letermovir for cytomegalovirus infection prophylaxis concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see section 4.4 and 4.5).

Use of 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 elderly (see section 5.2).

Paediatric population
The safety and efficacy of Ezetimibe/Atorvastatine DOC in children and adolescents below the age of 18 years have not yet been established (see section 5.1). No data are available.

Hepatic impairment
Ezetimibe/Atorvastatine DOC is not recommended in patients with moderate or severe hepatic impairment (Child Pugh >7, see sections 4.4 and 5.2). Ezetimibe/Atorvastatine DOC 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
For oral use.
Ezetimibe/Atorvastatine DOC can be administered as a single dose at any time of the day, with or without food.

4.3 Contraindications

Ezetimibe/Atorvastatine DOC is contraindicated:
in patients with hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- in patients with active liver disease or unexplained, persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN).
- during pregnancy and breast-feeding, and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6).
- in patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

Myopathy/Rhabdomyoleysis
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/Atorvastatine DOC 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/Atorvastatine DOC should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported

Before treatment
Ezetimibe/Atorvastatine DOC 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 a 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.
- If such symptoms occur whilst a patient is receiving treatment with Ezetimibe/Atorvastatine DOC,

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 atorvastatin or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.
- Ezetimibe/Atorvastatine DOC 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, positive anti-HMG CoA reductase antibody and improvement with immunosuppressive agents..

Concomitant treatment with other medicinal products
Due to the atorvastatin component of Ezetimibe/Atorvastatine DOC, the risk of rhabdomyolysis is increased when Ezetimibe/Atorvastatine DOC 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, niacin, or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products. (See section 4.8.)

In cases where coadministration of these medicinal products with Ezetimibe/Atorvastatine DOC 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/Atorvastatine DOC is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin 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/Atorvastatine DOC and fusidic acid should only be considered on a case by case basis and under close medical supervision.

<u>Liver enzymes</u>
In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥3 times 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 ULN persist, reduction of dose or withdrawal of Ezetimibe/Atorvastatine DOC is recommended.

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

Hepatic impairment
Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, Ezetimibe/Atorvastatine DOC is not recommended (see section 5.2).

Fibrates
The safety and efficacy of ezetimibe administered with fibrates have not been established. Therefore, concomitant treatment with Ezetimibe/Atorvastatine DOC is not recommended (see section 4.5).

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

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

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>30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Excipients
This medicine contains sucrose as sugar spheres. Each Ezetimibe/Atorvastatine DOC 10 mg/10 mg capsule contains 13 mg, each Ezetimibe/Atorvastatine DOC 10 mg/20 mg capsule contains 26 mg and each Ezetimibe/Atorvastatine DOC 10 mg/40 mg capsule contains 51.5 mg sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Atorvastatin, a component of Ezetimibe/Atorvastatine DOC, is metabolized 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 efflux transporters P-glycoprotein (P-gp) 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 atorvastatin 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/Atorvastatine DOC
No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with atorvastatin.

Effects of other medicinal products on Ezetimibe/Atorvastatine DOC

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.

Colestyramine: Concomitant colestyramine 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/Atorvastatine DOC to colestyramine 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/min on 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 medications, 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 ezetimib in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving Ezetimibe/Atorvastatine DOC and ciclosporin (see section 4.4).

Fibrates: Concomitant fenofibrate or gemfibrozil administration modestly increased total ezetimibe concentrations (approximately 1.5- and 1.7-fold, respectively). Although these increases are not considered clinically significant, coadministration of Ezetimibe/Atorvastatine DOC with fibrates is not recommended.

Atorvastatin

CYP3A4 inhibitors: Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Coadministration 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 coadministration of these medicinal products with atorvastatin cannot be avoided, lower starting and maximum doses of atorvastatin 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 coadministration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin 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/Atorvastatine DOC should not exceed 10 mg/20 mg daily in patients receiving concomitant medications with products containing elbasvir or grazoprevir (see section 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 coadministration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations. 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.

Transporter 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 exposure in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).

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. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

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 coadministered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were coadministered 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, Ezetimibe/Atorvastatine DOC treatment should be discontinued throughout the duration of the fusidic acid treatment (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.

Boceprevir: Exposure to atorvastatin was increased when administered with boceprevir. When coadministration with atorvastatin is required, starting with the lowest possible dose of atorvastatin should be considered with titration up to desired clinical effect while monitoring for safety, without exceeding a daily dose of 20 mg atorvastatin. For patients currently taking Ezetimibe/Atorvastatine DOC, the dose of Ezetimibe/Atorvastatine DOC should not exceed a daily dose of 10 mg/20 mg during coadministration with boceprevir (see Table 1).

Effects of Ezetimibe/Atorvastatine DOC 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 medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N- acetyltransferase.

In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, oral contraceptives (ethinyl estradiol and levonorgestrel), glipizide, tolbutamide, or midazolam during co-administration.
Cimetidine, co-administered with ezetimibe, had no effect on the bioavailability of ezetimibe.

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/Atorvastatine DOC 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 coadministered, steady-state digoxin concentrations increased slightly. Patients taking digoxin should be monitored appropriately.

Oral contraceptives: Coadministration 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, coadministration 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 atorvastatin 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

atorvastatin 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 coadministered 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	
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).
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 coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 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	3.4	
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 1400 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.
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.
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	1.74	No specific recommendation.
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.
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
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	0.20	

			clinical monitoring.
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 coadministration with boceprevir.

& Represents ratio of treatments (co-administered medicine 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 metabolized 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 hours 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
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 micrograms	 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 1400 mg BID, 14 days	0.73	No specific recommendation
10 mg, OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14	0.99	No specific recommendation.

	days		

& Represents ratio of treatments (co-administered medicine 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

Ezetimibe/Atorvastatine DOC is contraindicated during pregnancy (see section 4.3). No clinical data are available on the use of Ezetimibe/Atorvastatine DOC during pregnancy.

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).

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 fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.
For these reasons, atorvastatin should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with atorvastatin should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

Breast-feeding
Ezetimibe/Atorvastatine DOC is contraindicated during breast-feeding (see section 4.3).

Ezetimibe
Studies on rats have shown that ezetimibe is secreted into breast milk. It is not known if ezetimibe is secreted into human breast milk.

Atorvastatin
It is unknown whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3).

Fertility
No clinical data are available on the effects of Ezetimibe/Atorvastatine DOC on human fertility.

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

4.7 Effects on ability to drive and use machines

Ezetimibe/Atorvastatine DOC 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
Coadministration of ezetimibe and atorvastatin has been evaluated for safety in more than 2400 patients in 7 clinical trials.

Tabulated list of adverse reactions
Frequencies are defined as: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (frequency cannot be estimated from the available data).

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	nasopharyngitis[1]				
Blood and lymphatic system disorders			thrombocytopenia[1]		thrombocytopenia[2]
Immune system disorders	allergic reactions[1]			anaphylaxis[1]	hypersensitivity, including rash, urticaria, anaphylaxis and angio-oedema[2]
Metabolism and nutrition disorders	hyperglycemia[1]	hypoglycemia[1], weight gain[1], anorexia[1], decreased appetite[2]			
Psychiatric disorders		nightmare[1], insomnia[1]			depression[2]
Nervous system disorders	headache[1,3]	dizziness[1], paresthesia[1,3], hypoesthesia[1], dysgeusia[1], amnesia[1]	peripheral neuropathy[1]		dizziness2 myasthenia gravis
Eye disorders		vision blurred[1]	visual disturbance[1]		ocular myasthenia
Ear and labyrinth disorders		tinnitus[1]		hearing loss[1]	
Vascular Disorders		hot flush[2], hypertension[2]			
Respiratory, thoracic and mediastinal disorders	pharyngolaryngeal pain[1], epistaxis[1]	cough[2]			dyspnoea[2]
Gastrointestinal disorders	constipation[1], flatulence[1,2], dyspepsia[1], nausea[1], diarrhoea[1,2],	vomiting[1], abdominal pain upper and lower[1], eructation[1],			pancreatitis[2], constipation[2]

	abdominal pain[2]	pancreatitis[1], dyspepsia[2], gastroesophageal reflux disease[2], nausea[2], dry mouth[2], gastritis[2]			
Hepatobiliary disorders		hepatitis[1]	cholestasis[1]	hepatic failure[1]	hepatitis[2], cholelithiasis[2], cholecystitis[2]
Skin and subcutaneous tissue disorders		urticaria[1,3], pruritus[1,3], skin rash[1,3], alopecia[1]	angioneurotic oedema[1], dermatitis bullous including erythema multiforme, Stevens-Johnson's syndrome and toxic epidermal necrolysis[1]		erythema multiforme[2]
Musculoskeletal and connective tissue disorders	myalgia[1,2], arthralgia[1], pain in extremity[1], muscle spasms[1], joint swelling[1], back pain[1]	neck pain[1,2], muscle fatigue[1,2], arthralgia[2], muscle spasms[2], back pain[2], pain in extremity[2]	myopathy[1], myositis[1], rhabdomyolysis[1], muscle rupture[1], tendonopathy sometimes complicated by rupture[1]	lupus-like syndrome[1]	immune-mediated necrotizing myopathy[1], myopathy/rhabdomyolysis[2] (see section 4.4)
Reproductive system and breast disorders				gynecomastia[1]	
General disorders and administration site conditions	fatigue[2]	malaise[1], asthenia[1,2], chest pain[1,2], pain[2], peripheral oedema[1,2], fatigue[1], pyrexia[1]			
Investigations	liver function test abnormal[1], blood creatine kinase increased[1], ALT and/or AST increased[3]	white blood cells urine positive[1], blood creatine kinase increased[2], gamma-glutamyltransferase increased[2], liver function test abnormal[2]			

[1] Reported with atorvastatin
[2] Adverse reactions observed in clinical studies of ezetimibe (as a monotherapy or co-administered with a statin) or ezetimibe reported from post-marketing use either administered alone or with a statin. Adverse reactions were observed in patients treated with ezetimibe (n = 2396) and at a greater incidence than placebo (n = 1159) or in patients treated with ezetimibe co-administered with a statin (n = 11 308) and at a greater incidence than statin administered alone (n = 9361). Post-marketing Adverse reactions were derived from reports containing ezetimibe either administered alone or with a statin

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 het Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl.

4.9 Overdose

Ezetimibe/Atorvastatine DOC
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 hypercholesterolaemia 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/Atorvastatine DOC 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/Atorvastatine DOC
Plasma cholesterol is derived from intestinal absorption and endogenous synthesis.
Ezetimibe/Atorvastatine DOC contains ezetimibe and atorvastatin, two lipid-lowering compounds with complementary mechanisms of action. Ezetimibe/Atorvastatine DOC 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 selectively inhibits the intestinal absorption of cholesterol and related sterols. 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 [14C]-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 catabolized 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, ezetimibe either as monotherapy or co-administered with a statin 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 coadministered ezetimibe and

atorvastatin (10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg) for up to 12-weeks.

Patients receiving all doses of ezetimibe and atorvastatin were compared to those receiving all doses of atorvastatin. Ezetimibe and atorvastatin lowered total-C, LDL-C, Apo B, TG, and non-HDL-C, and increased HDL-C significantly more than atorvastatin alone.

In a double-blind, placebo-controlled, 8-week study, 769 patients with hypercholesterolaemia already receiving statin monotherapy and not at National Cholesterol Education Program (NCEP) LDL-C goal (2.6 to 4.1 mmol/l [100 to 160 mg/dl], depending on baseline characteristics) were randomised to receive either ezetimibe 10 mg or placebo in addition to their on-going statin therapy.

Among statin-treated patients not at LDL-C goal at baseline (~82%), significantly more patients randomised to ezetimibe achieved their LDL-C goal at study endpoint compared to patients randomised to placebo, 72% and 19%, respectively. The corresponding LDL-C reductions were significantly different (25% and 4% for ezetimibe versus placebo, respectively). In addition, ezetimibe, added to on-going statin therapy, significantly decreased total-C, Apo B, TG and increased HDL-C, compared with placebo. Ezetimibe or placebo added to statin therapy reduced median C-reactive protein by 10% or 0% from baseline, respectively.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Ezetimibe/Atorvastatine DOC 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/Atorvastatine DOC
Ezetimibe/Atorvastatine DOC has been shown to be bioequivalent to coadministration 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 (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 metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized 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.

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 impairment (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 impairment (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic impairment. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score > 9) hepatic impairment, 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 (Childs-Pugh B).

Renal impairment
Ezetimibe
After a single 10 mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl $\leq$30 mL/min/1.73 m^2), the mean AUC for total ezetimibe was increased approximately 1.5-fold, compared to healthy subjects (n=9). This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.
An additional patient in this study (post-renal transplant and receiving multiple medications, including 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

Ezetimibe/Atorvastatine DOC
In co-administration studies with ezetimibe and statins 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 2000 times the AUC level for the active metabolites).
In a series of *in vivo* and *in vitro* assays, ezetimibe, given alone or coadministered with statin, 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.

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. The co-administration of ezetimibe with lovastatin resulted in embryolethal effects.

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 $AUC_{0\text{-}24h}$ 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 fetuses. 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

Core:
Calcium carbonate (E170)
Hydroxypropylcellulose (E463)
Polysorbate 80 (E433)
Croscamellose sodium (E468)
Sugar spheres
Talc (E553B)
Mannitol (E421)
Microcrystalline cellulose (E460(i))
Low-substituted hydroxypropyl cellulose (E463)
Povidone (E1201)
Sodium laurilsulfate (E487)
Magnesium stearate (E572)

Capsule shell:

Ezetimibe/Atorvastatine DOC 10 mg/10 mg hard capsules:
Cap: Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Black iron oxide (E172), Gelatine (E441)
Body: Titanium dioxide (E171), Yellow iron oxide (E172), Gelatine (E441)

Ezetimibe/Atorvastatine DOC 10 mg/20 mg hard capsules:
Cap: Titanium dioxide (E171), Red iron oxide (E172), Gelatine (E441)
Body: Titanium dioxide (E171), Yellow iron oxide (E172), Gelatine (E441)

Ezetimibe/Atorvastatine DOC 10 mg/40 mg hard capsules:
Cap: Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Black iron oxide (E172), Gelatine (E441)
Body: Titanium dioxide (E171), Yellow iron oxide (E172), Gelatine (E441)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 °C in the original packaging in order to protect from moisture.

6.5 Nature and contents of container

30 hard capsules in OPA/Al/PVC//Al blister enclosed in folded cardboard box.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

DOC Generici Srl
Via Turati 40
20121 Milaan
Italië

8. MARKETING AUTHORISATION NUMBER(S)

10 mg/10 mg: RVG 125511
10 mg/20 mg: RVG 125512
10 mg/40 mg: RVG 125513

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 26 mei 2020
Datum van laatste verlenging: 31 oktober 2024

10. DATE OF REVISION OF THE TEXT

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