1. NAME OF THE MEDICINAL PRODUCT

Ezetimibe/Atorvastatine Sandoz 10 mg/10 mg, filmomhulde tabletten
Ezetimibe/Atorvastatine Sandoz 10 mg/20 mg, filmomhulde tabletten
Ezetimibe/Atorvastatine Sandoz 10 mg/40 mg, filmomhulde tabletten
Ezetimibe/Atorvastatine Sandoz 10 mg/80 mg, filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{[Nationally completed name]} 10 mg/ 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of ezetimibe and 10 mg of atorvastatin (as calcium trihydrate).

{[Nationally completed name]} 10 mg/ 20 mg film-coated tablets
Each film-coated tablet contains 10 mg of ezetimibe and 20 mg of atorvastatin (as calcium trihydrate).

{[Nationally completed name]} 10 mg/ 40 mg film-coated tablets
Each film-coated tablet contains 10 mg of ezetimibe and 40 mg of atorvastatin (as calcium trihydrate).

{[Nationally completed name]} 10 mg/ 80 mg film-coated tablets
Each film-coated tablet contains 10 mg of ezetimibe and 80 mg of atorvastatin (as calcium trihydrate).

Excipients with known effect
Each [Nationally completed name] 10 mg/ 10 mg film-coated tablet contains 2.74 mg of lactose.
Each [Nationally completed name] 10 mg/ 20 mg film-coated tablet contains 3.76 mg of lactose.
Each [Nationally completed name] 10 mg/ 40 mg film-coated tablet contains 5.81 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

{[Nationally completed name]} 10 mg/ 10 mg film-coated tablets
White, round, biconvex film-coated tablets, with diameter 8.1 mm approximately

{[Nationally completed name]} 10 mg/ 20 mg film-coated tablets
White, ovaloid, biconvex film-coated tablets, with dimensions 11.6 x 7.1 mm approximately

{[Nationally completed name]} 10 mg/ 40 mg film-coated tablets
White, capsule shape, biconvex film-coated tablets, with dimensions 16.1 x 6.1 mm approximately

{[Nationally completed name]} 10 mg/ 80 mg film-coated tablets
Yellow, oblong, biconvex film-coated tablets, with dimensions 19.1 x 7.6 mm approximately

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
[Nationally completed name] as an adjunct to diet is indicated as substitution therapy for treatment of adults with primary (heterozygous and homozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia already controlled with atorvastatin and ezetimibe given concurrently at the same dose level, but as separate products.

4.2 Posology and method of administration

Posology
The recommended dose of [Nationally completed name] is 1 tablet per day.
The maximum recommended dose of [Nationally completed name] is 10 mg/80 mg per day.
The patient should be on an appropriate lipid lowering diet and should continue on this diet during treatment with [Nationally completed name].

[Nationally completed name] is 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.
Elderly people
No dose adjustment is required for elderly patients (see section 5.2).

Paediatric population
The safety and efficacy of [Nationally completed name] in children and adolescent has not been established (see section 5.2). No data are available.

Patients with hepatic impairment
[Nationally completed name] is not recommended in patients with moderate or severe hepatic impairment (Child Pugh ≥7, see section 4.4. and 5.2). [Nationally completed name] is contraindicated in patients with active liver disease (see section 4.3).

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

Co-administration with bile acid sequestrants
Dosing of [Nationally completed name] should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant.

Coadministration with other medicines
In patients taking 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).

Method of administration
[Nationally completed name] is for oral administration. The tablet should be swallowed with a sufficient amount of fluid (e. g. one glass of water).
[Nationally completed name] can be administered as a single dose at any (but preferable always the same) 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 [Nationally completed name] is contraindicated during pregnancy and breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

[Nationally completed name] is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases exceeding 3 times the upper limit of normal (ULN) and 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.
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. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including atorvastatin. IMNM is clinically characterised by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia (see section 4.8). [Nationally completed name] 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
[Nationally completed name] should be prescribed with caution to patients with pre-disposing factors for rhabdomyolysis. ACPK 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 (>5times 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 other cause of CPK increase as it 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.

Monitoring during treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by mailaise or fever or if muscle signs and symptoms persist after discontinuing [Nationally completed name].
- If such symptoms occur whilst a patient is receiving treatment with [Nationally completed name], 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 [Nationally completed name] or introduction of another statin-containing product may be considered at the lowest dose and with close monitoring.
- [Nationally completed name] must be discontinued if clinically significant elevation of CPK levels (>10 times ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Simultaneous treatment with other products
Due to the atorvastatin component of [Nationally completed name], the risk of rhabdomyolysis is increased when atorvastatin 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, declavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, ledipasvir/sofosbuvir etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where coadministration of these medicinal products with [Nationally completed name] 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 [Nationally completed name] is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of [Nationally completed name] should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

[Nationally completed name] 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 infection, the need for co-administration of [Nationally completed name] and fusidic acid should only be considered on a case by case basis and under close medical supervision.

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

<u>Liver Enzymes</u>

In controlled coadministration trials in patients receiving ezetimibe and a statin, 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 transaminase of greater than 3 times the ULN persist, reduction of dose or withdrawal of [Nationally completed name] is recommended.

[Nationally completed name] 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, the administration of [Nationally completed name] 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 [Nationally completed name] is not recommended (see section 4.5).

Ciclosporin
Caution should be exercised when initiating [Nationally completed name] in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving [Nationally completed name]and ciclosporin (see section 4.5.).

Anticoagulants
If [Nationally completed name] 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 ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic 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 disontinued.

Diabetes mellitus
Some evidence suggests that statins as a class raise blood glucose and in some patients, a 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/m2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

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

[Nationally completed name] contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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.

Pharmacokinetic interactions
No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with atorvastatin.

Effects of other medicinal products on [Nationally completed name]

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 absoprtion 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 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/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 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 coadministered ezetimibe on ciclosporin exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating [Nationally completed name] in the setting of ciclosporin. Ciclosporin concentrations should be monitored in patients receiving [Nationally completed name] 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 [Nationally completed name] with fibrates is not recommended.

Atorvastatin

Effect of co-administered medicinal products on atorvastatin

Atorvastatin 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 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 atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivativees and ezetimibe (see section 4.3 and 4.4.).

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 co-administration with [Nationally completed name] may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of [Nationally completed name] 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 concentration 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 [Nationally completed name] should not exceed 10/20 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.

Transport inhibitors:
Inhibitors of transport proteins (e.g.ciclosporin, letermovir) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction of [Nationally completed name] 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.

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 when colestipol was coadministered with atorvastatin (Relative concentration of atorvastatin: 0.74). However, the lipid decreasing 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, atorvastatin 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-aministered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

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

Boceprevir: Exposure to atorvastatin was increased when administered with boceprevir. When coadministration with [Nationally completed name] is required, starting with the lowest possible dose of [Nationally completed name] 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 [Nationally completed name], the dose of [Nationally completed name] should not exceed a daily dose of 10/20 mg during coadministration with boceprevir.

<u>Effects of [Nationally completed name] on the pharmacokinetics of other medicinal products</u>

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.
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 [Nationally completed name] is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section 4.4).

Atorvastatin

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

Oral conceptives: 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 co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product	Atorvastatin		
and dosing regimen	Dose (mg)	Ratio of AUC[&]	Clinical Recommendation[#]
Tipranavir 500 mg BID/ Ritonavir	40 mg on day 1,	9.4	In cases where

200 mg BID, 8 days (days 14 to 21)	10 mg on day 20		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 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	
Nelfinavir 1250 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.
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.
Glecaprevir 400 mg OD/	10 mg OD	8.3	Co-administration with

Pibrentasvir 120 mg OD, 7 days	For 7 days		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.
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 refampin 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.
ledipasvir+sofusbuvir	Not known	↑ Statins	Interactions cannot be excluded with other HMG-CoA reductase inhibitors and ledipasvir+sofusbuvir.When statins are co-administered with ledipasvir+sofusbuvir, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 4.4).

[&] 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
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 1400 mg BID, 14	0.73	No specific recommendation.

	days		
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
[Nationally completed name] is contraindicated during pregnancy (see section 4.3). No clinical data are available on the use of [Nationally completed name] during pregnancy.

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.

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).

Breastfeeding
[Nationally completed name] is contraindicated during breast-feeding (see section 4.3).

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).

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.

Fertility
No clinical data are available on the effects of [Nationally completed name] on human fertility.

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

4.7 Effects on ability to drive and use machines

[Nationally completed name] 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

Frequencies are defined as: very common (≥1/10); common ≥1/100, < 1/10); uncommon (≥1/1000, < 1/100); rare (≥1/10,000, < 1/1000); and 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	-	-
Blood and lymphatic disorders	Thrombocytopenia	Rare	Not known*	-
Immune system disorder	Allergic reactions	Common	-	-
	Anaphylactic reactions	Very rare	-	-
	Hypersensitivity, including rash, urticarial, anaphylaxis and angio-oedema	-	Not known*	-
Metabolism and nutrition disorders	Hyperglycaemia	Common	-	-
	Hypoglycaemia, weight gain, anorexia	Uncommon	-	-
	Decreased appetite	-	Uncommon	-
Psychiatric disorders	Nightmare, insomnia	Uncommon	-	-
	Depression	-	Not known*	-
Nervous system disorder	Headache	Common	-	Common
	Dizziness	Uncommon	Not known*	-

	Hypoesthesia, dysgeusia, amnesia	Uncommon	-	-
	Paraesthesia	Uncommon	Not known*	Uncommon
	Peripheral neuropathy	Rare	-	-
	Myasthenia gravis	Not known	-	Not known
Eye disorders	Vision blurred	Uncommon	-	-
	Visual disturbance	Rare	-	-
	Ocular myasthenia	Not known	-	Not known
Ear and labyrinth disorders	Tinnitus	Uncommon	-	-
	Hearing loss	Very rare	-	-
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain, epistaxis	Common	-	-
	Cough	-	Uncommon	-
	Dyspnoea	-	Not known*	-
Gastrointestinal disorders	Flatulence, diarrhoea	Common	Common	-
	Constipation	Common	Not known*	-
	Nausea, dyspepsia	Common	Uncommon	-
	Vomiting, eructation	Uncommon	-	-
	Pancreatitis	Uncommon	Not known*	-
	Abdominal pain	Uncommon	Common	-
	Gastrooesophageal reflux disease	-	Uncommon	-
	Dry mouth, gastritis	-	-	Uncommon
Hepatobiliary disorders	Hepatitis	Uncommon	Not known*	-
	Cholestasis	Rare	-	-
	Hepatic failure	Very rare	-	-
	Cholelithiasis, cholecystitis	-	Not known*	-
Skin and subcutaneous tissue disorders	Urticaria, skin rash, pruritus	Uncommon	-	Uncommon
	Alopecia	Uncommon	-	-
	Angioneurotic oedema, dermatitis bullous including Stevens-Johnson syndrome and toxic epidermal necrolysis	Rare	-	-
	Erythema multiforme	Rare	Not known*	-
Musculoskeletal and connective tissue disorders	Arthralgia, muscle spasms	Common	Uncommon	-
	Joint swelling	Common	-	-
	Pain in extremity, back pain	Common	-	Uncommon
	Muscle fatigue	Uncommon	-	-
	Muscular weakness	Uncommon	-	Uncommon
	Neck pain	Uncommon	Uncommon	-
	Myalgia	Common	Not known*	Common

	Myositis, tendinopathy (sometimes complicated by rupture)	Rare	-	-
	Immune-mediated necrotizing myopathy	Not known	-	-
	Myopathy/rhabdomyolysis/ Muscle rupture	Rare	Not known*	-
	Lupus-like syndrome	Very rare	-	-
Reproductive system and breast disorders	Gynecomastia	Very rare	-	-
Vascular disorders	Hot flush, hypertension	-	Uncommon	-
General disorders and administration site conditions	Oedema peripheral	Uncommon	-	Uncommon
	Asthenia	Uncommon	Not known*	Uncommon
	Chest pain	Uncommon	Uncommon	-
	Fatigue	Uncommon	Common	-
	Malaise, pyrexia	Uncommon	-	-
	Pain	-	Uncommon	-
Investigations	Liver function test abnormal, blood creatine kinase increased	Common	-	-
	White blood cells urine positive	Uncommon	-	-
	ALT and/or AST increased	-	Uncommon	Common
	Blood CPK increased, gamma-glutamyltransferase increased, liver function test abnormal	-	Uncommon	-

* Post-marketing experience (with or without statin)

The following adverse events have been reported with some statins:
- sexual dysfunction
- depression
- 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, 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 national reporting system listed in Appendix V.

4.9 Overdose

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 anmimals, no toxicity was observed after single oral doses of 5000 mg/kg of ezetimibe in rats and mice and 3000 mg/kg in dogs.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
High blood cholesterol levels are derived from intestinal absorption and endogenous cholesterol biosynthesis. [Nationally completed name] contains ezetimibe and atorvastatin, two lipid lowering compounds with complementary mechanisms of action.

Ezetimibe
Ezetimibe is in a new class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related plant 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, in contrast, is a selective, competitive inhibitor of the cholesterol biosynthesis in the liver. It inhibits the 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), so called transport proteins. These transport proteins are released into the plasma for delivery of cholesterol to peripheral tissues. Low-density lipoproteins (LDL) are formed from VLDL and are catabolized primarily through the receptor with a high affinity to LDL.

Atorvastatin lowers plasma cholesterol and lipoprotein in serum concentrations by inhibiting the 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. The results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

The combination product reduces therefore 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.

Clinical Efficacy

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 < 2mmol/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 (Ai, 2018) of combination therapy of ezetimibe and atorvastatin vs. atorvastatin monotherapy 17 trials with 5,206 participants were analyzed. All trials were randomized, parallel-group studies of more than 4 weeks duration and 9 trials were double-blind. Patients with LDL-C level > 70 mg/dL (1.81 mmol/L) (at high risk of CHD) or with hypercholesterolaemia were included in the trials. The change of LDL-C, HDL-C and TC were investigated in 17 studies while 15 studies reported the TG changes. The comparisons also included 4 doses: 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 was significant, on lowering LDL-C (mean difference (MD) = −15.38, 95% CI: −16.17 to −14.60; I^2 = 26.2%, n = 17 studies), on TC (MD = −9.51, 95% CI: −10.28 to −8.74; I^2 = 33.7%, n = 17 studies) and on TG (MD = −6.42, 95% CI: −7.78 to − 5.06; I^2 = 0%, n = 15 studies). Also, the efficacy of the combination on raising HDL-C (MD = 0.95, (95% CI: 0.34 to 1.57; I^2 = 0%, n = 17 studies) was overall significant.

5.2 Pharmacokinetic properties

The combination product 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 (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 at 10 mg tablets.

Atorvastatin

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1-2 hours. Exent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin 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 readioactivity 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 a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1

(MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin. 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 of HMG-CoA reductase is approximately 20-30 hours due to the contribution of active metabolites.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with [Nationally completed name] in all subsets of the paediatric population.

Ezetimibe
The absorption and metabolism of ezetimibe are similar between children and adolescents (10 to 18 years) and adults. Based on total ezetimibe, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the paediatric population < 10 years of age are not available.

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 hypercholesterolemia and baseline LDL-C ≥ 4 mmol/L were treated with 5 or 10 mg of chewable or 10 or 20 mg of atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model.
Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Elderly

Ezetimibe
Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and younger subjects treated with ezetimibe.

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

Hepatic impairment
Ezetimibe
After a single 10-mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1.7-fold in patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency

(Child-Pugh score 7 to 9), the mean AUC for total ezetimibe was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dose adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child-Pugh score > 9) hepatic insufficiency, ezetimibe is not recommended in these patients (see sections 4.2 and 4.4).

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

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

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

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

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

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

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

are unknown.

5.3 Preclinical safety data

Ezetimibe
Animal studies on the chronic toxicity of ezetimibe identified no target organs for toxic effect. In dogs treated for four weeks with ezetimibe (≥0.03 mg/kg/day) the cholesterol concentration in the cystic bile was increased by a factor of 2.5 to 3.5. However, in a one year study on dogs given doses of up to 300 mg/kg/day no increased incidence of cholelithiasis or other hepatobiliary effects were observed. The significance of these data for humans is not known. A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out. Long-term carcinogenicity tests on ezetimibe were negative. Ezetimibe had no effect on the fertility of male or female rats, nor was it found to be teratogenic in rats or rabbits, nor did it affect prenatal or postnatal development. Ezetimibe crossed the placental barrier in pregnant rats and rabbits given multiple doses of 1000 mg/kg/day.

Atorvastatin
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 *in vitro* tests and 1 *in vivo* assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24 h reached in humans at the highes 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.

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 2000 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
Cellulose Microcrystalline 101 (E460)
Mannitol (E 421)
Calcium carbonate (E170)
Croscarmellose sodium (E468)
Hydroxypropylcellulose (E463)
Polysorbate 80 (E433)
Iron oxide yelllow (E172)
Magnesium stearate (E470b)
Povidone K29/32 (E1201)
Sodium laurilsulfate (E487)

Tablet Coating
[Nationally completed name] 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg - Opadry White OY-L-28900 consisting of:
Lactose monohydrate
Hypromellose 2910 (E464)
Titanium dioxide (E171)
Macrogol 4000 (E1521)

[Nationally completed name] 10 mg/80 mg - DrCoat FCU consisting of:
Hypromellose 2910
Titanium dioxide (E171)
Talc (E553b)
Macrogol 400
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

[Nationally completed name] 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg film-coated tablets
OPA/Al/PVC//Al blisters containing 10, 30, 90 and100 film-coated tablets.
OPA/Al/PVC//Al perforated unit-dose blisters of 10 × 1, 30 × 1, 90 × 1 and 100 × 1 film-coated tablets.

[Nationally completed name] 10 mg/80 mg film-coated tablets
OPA/Al/PVC//Al blisters containing 10, 30, multipack containing 90 (2 packs of 45) and multipack containing 100 (2 packs of 50) film-coated tablets.
OPA/Al/PVC//Al perforated unit-dose blisters of 10 x 1, 30 x 1, multipack containing 90 x1 (2 packs of 45 x 1) and multipack containing 100 x 1 (2 packs of 50 x 1) film-coated tablets.

Not all pack sizes may be marketed.

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. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMERS VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Ezetimibe/Atorvastatine Sandoz 10 mg/10 mg, filmomhulde tabletten - RVG 126886
Ezetimibe/Atorvastatine Sandoz 10 mg/20 mg, filmomhulde tabletten - RVG 126887
Ezetimibe/Atorvastatine Sandoz 10 mg/40 mg, filmomhulde tabletten - RVG 126888
Ezetimibe/Atorvastatine Sandoz 10 mg/80 mg, filmomhulde tabletten - RVG 126889

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 26 oktober 2021
Datum van laatste verlenging: 26 september 2026

10. DATUM VAN HERZIENING VAN DE TEKST

De laatste gedeeltelijke wijziging betreft rubriek 9: 26 februari 2026