SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[Product name] 10 mg film-coated tablets
[Product name] 20 mg film-coated tablets
[Product name] 40 mg film-coated tablets
[Product name] 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg atorvastatin (as atorvastatin calcium trihydrate).
Excipient with known effect:
Each film-coated tablet contains 11.990 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

Each film-coated tablet contains 20 mg atorvastatin (as atorvastatin calcium trihydrate).
Excipient with known effect:
Each film-coated tablet contains 23.980 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

Each film-coated tablet contains 40 mg atorvastatin (as atorvastatin calcium trihydrate).
Excipient with known effect:
Each film-coated tablet contains 47.960 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

Each film-coated tablet contains 80 mg atorvastatin (as atorvastatin calcium trihydrate).
Excipient with known effect:
Each film-coated tablet contains 95.920 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
[Product name] 10 mg film-coated tablets: White to off white, film-coated, round, biconvex tablet. Diameter of the tablet is approx. 6 mm.
[Product name] 20 mg film-coated tablets: Yellowish, film-coated, round, biconvex tablet. Diameter of the tablet is approx. 8 mm.
[Product name] 40 mg film-coated tablets: Orange-yellow to yellow-orange, film-coated, round, biconvex tablet. Diameter of the tablet is approx. 10 mm.
[Product name] 80 mg film-coated tablets: Yellow-orange film-coated round, biconvex tablet. Diameter of the tablet is approx. 12 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia
[Product name] is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

[Product name] is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention of cardiovascular disease
Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.

4.2 Posology and method of administration

Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving [Product name] and should continue on this diet during treatment with [Product name].

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with [Product name] 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia
Patients should be started with [Product name] 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia
Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment
No adjustment of dose is required (see section 4.4).

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

Elderly
Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric population

Hypercholesterolaemia
Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.

For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day (see section 5.1). The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualised according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg daily is supported by study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia (see sections 4.8 and 5.1).

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Other pharmaceutical forms/strengths may be more appropriate for this population.

Method of administration
[Product name] is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

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

4.3 Contraindications

[Product name] is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).
- treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

4.4 Special warnings and precautions for use

Liver effects
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of [Product name] is recommended (see section 4.8).

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

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 haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

Skeletal muscle effects
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 kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

There have been very rare reports of an immune-mediated necrotizing 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.

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin 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 CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

Creatine kinase measurement
Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult.
If CK 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 atorvastatin, their CK 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 CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CK levels (> 10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products
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. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin, or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin 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 atorvastatin 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 [Product name] and fusidic acid should only be considered on a case by case basis and under close medical supervision.

Paediatric population
No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight (see section 4.8).

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products

that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates 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). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatement of HCV (e.g. elbasvir/grazoprevir) and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medicinal products with 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 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.

CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport inhibitors

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

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

acid derivatives and atorvastatin. 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 (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

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

If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (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.

Effect of atorvastatin on co-administered medicinal products

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

Oral contraceptives
Co-administration of atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

Warfarin
In a clinical study in patients receiving chronic warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting 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.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Drug interactions

Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Ratio of AUC[&]	Clinical recommendation[#]
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).
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 co-administration 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

Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	3.4	atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Itraconazole 200 mg OD, 4 days	40 mg SD	3.3	
Fosamprenavir 700 mg BID/Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	2.5	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	2.3	
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, 28 weeks	40 mg OD for 28 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

Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	0.20	co-administration of atorvastatin with rifampin is recommended, with 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 co-administration with boceprevir.

[&]Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).
[#]See sections 4.4 and 4.5 for clinical significance.
*Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold.
** Ratio based on a single sample taken 8-16 h post dose.

OD = once daily; SD = single dose; BID = twice daily; TID = three times daily; QID = four times daily

Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Ratio of AUC[&]	Clinical recommendation
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 days	0.73	No specific recommendation
10 mg OD for 4 days	Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days	0.99	No specific recommendation

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.
OD = once daily; SD = single dose; BID = twice daily

4.6 Fertility, pregnancy and lactation

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

Pregnancy
[Product name] is contraindicated during pregnancy (see section 4.3). 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. Studies in animals 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, [Product name] should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with [Product name] 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
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). Because of the potential for serious adverse reactions, women taking [Product name] should not breast-feed their infants (see section 4.3). Atorvastatin is contraindicated during breast-feeding (see section 4.3).

Fertility
In animal studies atorvastatin had no effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

[Product name] has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8,755 atorvastatin vs. 7,311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for atorvastatin.

Estimated frequencies of reactions are ranked according to the following convention: 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 (cannot be estimated from the available data).

Infections and infestations
Common: nasopharyngitis.

Blood and lymphatic system disorders
Rare: thrombocytopenia.

Immune system disorders
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia.

Psychiatric disorders
Uncommon: nightmare, insomnia.

Nervous system disorders
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, muscle rupture, tendinopathy, sometimes complicated by rupture.
Very rare: lupus-like syndrome.
Not known: immune-mediated necrotizing myopathy (see section 4.4).

Reproductive system and breast disorders
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations
Common: liver function test abnormal**,** blood creatine kinase increased.
Uncommon: white blood cells urine positive.

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin - treated patients (see section 4.4).

Paediatric population
Paediatric patients aged from 10 to 17 years of age treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of

Tanner Stage, and measurement of height and weight. The safety and tolerability profile in paediatric patients was similar to the known safety profile of atorvastatin in adult patients.

The clinical safety database includes safety data for 520 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 121 patients were in the age range of 6 to 9, and 392 patients were in the age range of 10 to 17. Based on the data available, the frequency, type and severity of adverse reactions in children is similar to adults.

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^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 the national reporting system listed in Appendix V.

4.9 Overdose

Specific treatment is not available for [Product name] overdose. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CK levels should be monitored. 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, ATC code: C10AA05

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

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

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

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.

Homozygous familial hypercholesterolaemia

In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double- blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin, the effects of atorvastatin were statistically significant (p=0.02). The effect of intensive lipid lowering on cardiovascular endpoints (e. g. need for revascularisation, non fatal myocardial infarction, coronary death) was not investigated in this study.

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/l ± 0.8 (78.9 mg/dl ± 30) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/L ± 0.7 (110 mg/dl ± 26) from baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22.0%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: + 5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

Study results were obtained with the 80 mg dose strength. Therefore, they cannot be extrapolated to the lower dose strengths.

The safety and tolerability profiles of the two treatment groups were comparable.

The effect of intensive lipid lowering on major cardiovascular endpoints was not investigated in this study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Acute coronary syndrome

In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with evidence of myocardial ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

The safety profile of atorvastatin in the MIRACL study was consistent with what is described in section 4.8.

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomised, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC: HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular	20%	389 vs. 483	1.9%	0.0008

events and revascularization procedures				
Total coronary events	29%	178 vs 247	1.4%	0.0006

[1]Based on difference in crude events rates occurring over a median follow-up of 3.3 years. CHD = coronary heart disease; MI = myocardial infarction.

Total mortality and cardiovascular mortality were not significantly reduced (185 vs. 212 events, p=0.17 and 74 vs. 82 events, p=0.51). In the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females possibly due to the low event rate in the female subgroup. Overall and cardiovascular mortality were numerically higher in the female patients (38 vs. 30 and 17 vs. 12), but this was not statistically significant. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.47 (0.32-0.69), p=0.00008), but not in those treated with atenolol (HR 0.83 (0.59-1.17), p=0.287).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomised, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1,428) or placebo (n=1,410) for a median follow-up of 3.9 years.

The absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative Risk Reduction (%)	No of Events (Atorvastatin vs.Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs. 64	1.9%	0.0070
Strokes (fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

[1]Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p = 0.0592).

Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4,731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dl (3.4 mmol/l). The mean LDL-C was 73 mg/dl (1.9 mmol/l) during treatment with atorvastatin and 129 mg/dl (3.3 mmol/l) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, p=0.01) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 1.4%, p=0.02) compared to placebo.

• The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57), and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

• The risk of haemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior haemorrhagic stroke. All cause mortality was 10.9% (77/708) for atorvastatin versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct**.**

Paediatric Population

Heterozygous familial hypercholesterolaemia in paediatric patients aged 6-17 years old

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C ≥4 mmol/l. A

total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage ≥2.

The initial dose of atorvastatin was 5 mg daily of a chewable tablet in Cohort A and 10 mg daily of a tablet formulation in Cohort B. The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of <3.35 mmol/l at Week 4 and if atorvastatin was well tolerated.

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.

In a second open label, single arm study, 271 male and female HeFH children 6-15 years of age were enrolled and treated with atorvastatin for up to three years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level ≥ 4 mmol/l (approximately 152 mg/dl). The study included 139 children at Tanner 1 developmental stage (generally ranging from 6-10 years of age). The dosage of atorvastatin (once daily) was initiated at 5 mg (chewable tablet) in children less than 10 years of age. Children age 10 and above were initiated at 10 mg atorvastatin (once daily). All children could titrate to higher doses to achieve a target of < 3.35 mmol/l LDL-C. The mean weighted dose for children aged 6 to 9 years was 19.6 mg and the mean weighted dose for children aged 10 years and above was 23.9 mg.

The mean (+/- SD) baseline LDL-C value was 6.12 (1.26) mmol/l which was approximately 233 (48) mg/dl. See table 3 below for final results.

The data were consistent with no drug effect on any of the parameters of growth and development (i.e. height, weight, BMI, Tanner stage, Investigator assessment of Overall Maturation and Development) in paediatric and adolescent subjects with HeFH receiving atorvastatin treatment over the 3 year study. There was no Investigator-assessed drug effect noted in height, weight, BMI by age or by gender by visit.

Table 3 Lipid-lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)

Timepoint	N	TC (S.D.)	LDL-C (S.D.)	HDL-C (S.D.)	TG (S.D.)	Apo B (S.D.)#
Baseline	271	7.86(1.30)	6.12(1.26)	1.314(0.2663)	0.93(0.47)	1.42(0.28)**
Month 30	206	4.95(0.77)*	3.25(0.67)	1.327(0.2796)	0.79(0.38)*	0.90(0.17)*
Month 36/ET	240	5.12(0.86)	3.45(0.81)	1.308(0.2739)	0.78(0.41)	0.93(0.20)***

TC= total cholesterol; LDL-C = low density cholesterol-C; HDL-C = high density cholesterol-C; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month timepoint as well as full 36 month data for subjects competing the 36 month participation; "*"= Month 30 N for this parameter was 207; "**"= Baseline N for this parameter was 270; "***" = Month 36/ET N for this parameter was 243; "#"=g/L for Apo B.

Heterozygous familial hypercholesterolaemia in paediatric patients aged 10-17 years old

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26-week double-blind phase.

An additional paediatric study of atorvastatin versus colestipol in patients with hypercholesterolaemia aged 10-18 years demonstrated that atorvastatin (N=25) caused a significant reduction in LDL-C at week 26 ($p<0.05$) compared with colestipol (N=31).

A compassionate use study in patients with severe hypercholesterolaemia (including homozygous hypercholesterolaemia) included 46 paediatric patients treated with atorvastatin titrated according to response (some subjects received 80 mg atorvastatin per day). The study lasted 3 years: LDL-cholesterol was lowered by 36%.

The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0 to less than 6 years in the treatment of heterozygous hypercholesterolaemia and in children aged 0 to less than 18 years in the treatment of homozygous familial hypercholesterolaemia, combined (mixed) hypercholesterolaemia, primary hypercholesterolaemia and in the prevention of cardiovascular events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

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

Biotransformation

Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. *In vitro*, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Elimination

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

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

Special populations

Elderly

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.

Paediatric population

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 film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

Gender:

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.

Renal impairment

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

Hepatic impairment

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

SLOC1B1 polymorphism
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

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 *in vitro* tests and 1 *in vivo* assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11-fold the AUC_{0-24h} reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females.

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal 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
Cellulose, microcrystalline (E 460)
Lactose monohydrate
Low-substituted hydroxypropyl cellulose
Povidone K12
Silica, colloidal anhydrous
Magnesium stearate (E 572)

Coating
Hypromellose (E 464)
Macrogol 6000
Titanium dioxide (E 171)
Talc
Iron oxide yellow (E 172)
Lactose monohydrate

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

OPA/Al/PVC//Al blister
Pack sizes:
10 mg: 10, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
20 mg: 10, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
40 mg: 7, 10, 14, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
80 mg: 7, 10, 14, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

[Product name] 10 mg film-coated tablets
[Product name] 20 mg film-coated tablets
[Product name] 40 mg film-coated tablets
[Product name] 80 mg film-coated tablets

Atorvastatin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each [Product name] 10 mg film-coated tablet contains 10 mg atorvastatin as atorvastatin calcium trihydrate.

Each [Product name] 20 mg film-coated tablet contains 20 mg atorvastatin as atorvastatin calcium trihydrate.

Each [Product name] 40 mg film-coated tablet contains 40 mg atorvastatin as atorvastatin calcium trihydrate.

Each [Product name] 80 mg film-coated tablet contains 80 mg atorvastatin as atorvastatin calcium trihydrate.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10 mg:
10 film-coated tablets
14 film-coated tablets
15 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets

60 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
200 film-coated tablets

20 mg:
10 film-coated tablets
14 film-coated tablets
15 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
200 film-coated tablets

40 mg:
7 film-coated tablets
10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
200 film-coated tablets

80 mg:
7 film-coated tablets
10 film-coated tablets
14 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
60 film-coated tablets
90 film-coated tablets
98 film-coated tablets
100 film-coated tablets
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[Product name] 10 mg tablets
[Product name] 20 mg tablets
[Product name] 40 mg tablets
[Product name] 80 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[Product name] 10 mg film-coated tablets
[Product name] 20 mg film-coated tablets
[Product name] 40 mg film-coated tablets
[Product name] 80 mg film-coated tablets

Atorvastatin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Logo Zentiva

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

[Product name] 10 mg film-coated tablets
[Product name] 20 mg film-coated tablets
[Product name] 40 mg film-coated tablets
[Product name] 80 mg film-coated tablets

Atorvastatin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What [Product name] is and what it is used for

[Product name] belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.
[Product name] is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and lifestyle changes on their own have failed. If you are at an increased risk of heart disease, [Product name] can also be used to reduce such risk even if your cholesterol levels are normal. You should maintain a standard cholesterol lowering diet during treatment.

2. What you need to know before you take [Product name]

Do not take [Product name]
- if you are allergic to atorvastatin or any of the other ingredients of this medicine (listed in section 6).
- if you have or have ever had a disease which affects the liver.
- if you have had any unexplained abnormal blood tests for liver function.
- if you use the combination of glecaprevir/pibrentasvir in the treatment of hepatitis C.
- if you are a woman able to have children and not using reliable contraception.
- if you are pregnant or trying to become pregnant.
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor or pharmacist before taking [Product name]. The following are reasons why [Product name] may not be suitable for you:
- if you have severe respiratory failure
- if you are taking or have taken in the last 7 days a medicine called fusidic acid, (a medicine for bacterial infection) orally or by injection. The combination of fusidic acid and [Product name] can lead to serious muscle problems (rhabdomyolysis)
- if you have had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes
- if you have kidney problems
- if you have an under-active thyroid gland (hypothyroidism)
- if you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems
- if you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)
- if you regularly drink a large amount of alcohol
- if you have a history of liver disease
- if you are older than 70 years.

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your [Product name] treatment to predict your risk of muscle related side effects. The risk of muscle related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see section 2 "Other medicines and [Product name]").

Also tell your doctor or pharmacist if you have a muscle weakness that is constant. Additional tests and medicines may be needed to diagnose and treat this.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

Other medicines and [Product name]
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
There are some medicines that may change the effect of [Product name] or their effect may be changed by [Product name]. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the important muscle wasting condition known as rhabdomyolysis described in section 4:
- Medicines used to alter the way your immune system works, e.g. ciclosporin.
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid.
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, colestipol.
- Some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem; medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone.
- Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, atazanavir, indinavir, darunavir, the combination of tipranavir/ritonavir etc.

- Some medicines used in the treatment of hepatitis C e.g. telaprevir, boceprevir and the combination of elbasvir/grazoprevir.
- Other medicines known to interact with [Product name] include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stiripentol (an anticonvulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazone (a painkiller), colchicine (used to treat gout), and antacids (indigestion products containing aluminium or magnesium).
- Medicines obtained without a prescription: St. John's Wort.
- If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart [Product name]. Taking [Product name] with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in section 4.

[Product name] with food, drink and alcohol
See section 3 for instructions on how to take [Product name]. Please note the following:

Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of [Product name].

Alcohol
Avoid drinking too much alcohol while taking this medicine. See section 2 "Warnings and precautions" for details.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take [Product name] if you are pregnant or if you are trying to become pregnant.
Do not take [Product name] if you are able to become pregnant unless you use reliable contraceptive measures.
Do not take [Product name] if you are breast-feeding.
The safety of [Product name] during pregnancy and breast-feeding has not yet been proven.

Driving and using machines
Normally this medicine does not affect your ability to drive or operate machines. However, do not drive if this medicine affects your ability to drive. Do not use any tools or machines if your ability to use them is affected by this medicine.

[Product name] contains lactose monohydrate.
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take [Product name]

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with [Product name].

The usual starting dose of [Product name] is 10 mg once a day in adults and children aged 10 years or older. This may be increased if necessary by your doctor until you are taking the amount you need. Your doctor will adapt the dose at intervals of 4 weeks or more. The maximum dose of [Product name] is 80 mg once a day.
[Product name] tablets should be swallowed whole with a drink of water, and can be taken at any time of day, with or without food. However, try to take your tablet at the same time every day.

The duration of treatment with [Product name] is determined by your doctor.

Please ask your doctor if you think that the effect of [Product name] is too strong or too weak.

If you take more [Product name] than you should
If you accidentally take too many [Product name] tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take [Product name]
If you forget to take a dose, just take your next scheduled dose at the correct time.
Do not take a double dose to make up for a forgotten dose.

If you stop taking [Product name]
If you have any further questions on the use of this medicine or wish to stop your treatment, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following serious side effects or symptoms, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.

Rare: may affect up to 1 in 1,000 people:
- Serious allergic reaction which causes swelling of the face, tongue and throat that can cause great difficulty in breathing.
- Serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes, genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister.
- Muscle weakness, tenderness, pain, rupture or red-brown discolouration of urine and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown (rhabdomyolysis). The abnormal muscle breakdown does not always go away, even after you have stopped taking atorvastatin, and it can be life-threatening and lead to kidney problems.

Very rare: may affect up to 1 in 10,000 people:
- Lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

– If you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.

Other possible side effects with [Product name]:

Common side effects (may affect up to 1 in 10 people) include:
- inflammation of the nasal passages, pain in the throat, nose bleed
- allergic reactions
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase
- headache
- nausea, constipation, wind, indigestion, diarrhoea
- joint pain, joint swelling, muscle pain, muscle spasms, pain in arms and legs and back pain
- blood test results that show your liver function can become abnormal

Uncommon side effects (may affect up to 1 in 100 people) include:
- anorexia (loss of appetite), weight gain, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels)
- having nightmares, insomnia
- dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory
- blurred vision
- ringing in the ears and/or head
- vomiting, belching, abdominal pain upper and lower, pancreatitis (inflammation of the pancreas leading to stomach pain)
- hepatitis (liver inflammation)
- rash, skin rash and itching, hives, hair loss
- neck pain, muscle fatigue
- fatigue, feeling unwell, weakness, chest pain, swelling especially in the ankles (oedema), raised temperature
- urine tests that are positive for white blood cells

Rare side effects (may affect up to 1 in 1,000 people) include:
- visual disturbance
- unexpected bleeding or bruising
- cholestasis (yellowing of the skin and whites of the eyes)
- tendon injury

Very rare side effects (may affect up to 1 in 10,000 people) include:
- an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse
- hearing loss
- gynecomastia (breast enlargement in men)

Not known (frequency cannot be estimated from the available data):
- muscle weakness that is constant.

Possible side effects reported with some statins (medicines of the same type):
- sexual difficulties
- depression
- breathing problems including persistent cough and/or shortness of breath or fever
- diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Product name]

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer packaging after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Do not use this medicine if you notice visible signs of deterioration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What [Product name] contains
The active substance is atorvastatin.

Each film-coated tablet contains 10 mg atorvastatin (as atorvastatin calcium trihydrate).
Each film-coated tablet contains 20 mg atorvastatin (as atorvastatin calcium trihydrate).
Each film-coated tablet contains 40 mg atorvastatin (as atorvastatin calcium trihydrate).
Each film-coated tablet contains 80 mg atorvastatin (as atorvastatin calcium trihydrate).

The other ingredients are:
Core: Calcium carbonate, Cellulose, microcrystalline (E 460), Lactose monohydrate, Low-substituted hydroxypropyl cellulose, Povidone K12, Silica, colloidal anhydrous, Magnesium stearate (E 572).
Coating: Hypromellose (E 464), Macrogol 6000, Titanium dioxide (E 171), Talc, Iron oxide yellow (E 172), Lactose monohydrate.

What [Product name] looks like and contents of the pack
[Product name] 10 mg film-coated tablets are white to off white, film-coated, round, biconvex tablets. Diameter of the tablet is approx. 6 mm.

[Product name] 20 mg film-coated tablets are yellowish, film-coated, round, biconvex tablets. Diameter of the tablet is approx. 8 mm.
[Product name] 40 mg film-coated tablets are orange-yellow to yellow-orange, film-coated, round, biconvex tablet. Diameter of the tablet is approx. 10 mm.
[Product name] 80 mg film-coated tablets are yellow-orange film-coated round, biconvex tablets. Diameter of the tablet is approx. 12 mm.
Pack sizes:
10 mg: 10, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
20 mg: 10, 14, 15, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
40 mg: 7, 10, 14, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
80 mg: 7, 10, 14, 28, 30, 50, 56, 60, 90, 98, 100 or 200 film-coated tablets
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
[To be completed nationally]

Manufacturer
[To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

Bulgaria	Торвакард Зентива 10 mg/20 mg/40 mg/80 mg филмирани таблетки
Czech Republic	Torvacard Neo
Cyprus, Greece	Torvacard Neo
Estonia	Atorvastatin Zentiva 10 mg/20 mg/80 mg
France	Atorvastatine Zentiva 10 mg/20 mg/40 mg/80 mg, comprimé pelliculé
Hungary	Torvacard Zentiva 10 mg/20 mg/40 mg/80 mg filmtabletta
Italy, Malta	Atorvastatina Zentiva Italia
Latvia	Atorvastatin Zentiva 10 mg/20 mg/40 mg/80 mg apvalkotās tabletes
Lithuania	Atorvastatin Zentiva 10 mg/20 mg/80 mg plėvele dengtos tabletės
Poland	Torvacard neo
Portugal	Atorvastatina Zentiva
Romania	TORVACARD 10 mg/20 mg/40 mg/80 mg comprimate filmate
Slovak Republic	Torvacard Novum 10 mg/20 mg/40 mg/80 mg
Spain	Atorvastatina Zentiva Lab 10 mg/20 mg/40 mg/80 mg comprimidos recubiertos con película EFG
United Kingdom	Atorvastatin 10 mg/20 mg/40 mg/80 mg Film-coated Tablets

This leaflet was last revised in

[To be completed nationally]