SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

COLASTIN-L 20 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Atorvastatin calcium trihydrate ..... 21.651 mg
Equivalent to 20 mg Atorvastatin.

Excipient(s) with known effect:
Lactose monohydrate ..... 83.000 mg
Croscarmellose sodium ..... 19.000 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.
White, oblong, homogenous, film-coated tablets debossed “20” on one side and scored on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia
Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolemia including heterozygous hypercholesterolemia or combined (mixed) hyperlipidemia when response to diet and other non-pharmacological measures is inadequate. It increases HDL cholesterol and decreases LDL/HDL and total cholesterol/HDL ratios.

It is also indicated to reduce total cholesterol, LDL cholesterol and apolipoprotein B in adult patients with homozygous familial hypercholesterolemia as an adjunct to diet and other methods, when response to diet and other methods is inadequate.

Prevention of cardiovascular disease
Indicated for prevention of major cardiovascular events in patients estimated to have a high risk for cardiovascular events, 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 COLASTIN-L and should continue on this diet during treatment with COLASTIN-L. The dosage range is 10 to 80 mg once daily. The initial and maintenance doses of COLASTIN-L should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. After initiation and/or upon titration of treatment, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Primary hypercholesterolemia and combined hyperlipidemia
The majority of patients are controlled with atorvastatin 10 mg once a day. A therapeutic response is evident within 2 weeks following the initiation of treatment, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolemia
Patients should be started with 10 mg daily. Doses should be individualized, analyzed every 4 weeks and adjusted to 40 mg daily if required. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid-binding resin sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolemia
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.

Method of administration
For oral administration only. COLASTIN-L can be taken as a single dose at any time of the day with or without food.

Additional information on special populations
Renal impairment: Renal failure or renal disease has no influence on LDL-C reducing effect and plasma blood concentrations of atorvastatin; thus, dose adjustment in patients with renal dysfunction is not necessary (see section 4.4 and 5.2).

Hepatic impairment: See sections 4.3 and 4.4.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age)
Recommended initial dose of COLASTIN-L is 10 mg per day and maximum recommended dose is 20 mg per day (doses above 20 mg and combined treatment have not been studied in this patient population). Dosage should be individualized according to proposed treatment goal (see section 5). Adjustments should be made at intervals of at least 4 weeks.

Geriatric population
In terms of safety and efficacy, no differences were observed between elderly patients and the general population at recommended doses (see section 4.4).

Concomitant lipid-lowering therapy
COLASTIN-L may be used with a bile acid-binding resin for additive effect. The combination of HMG-CoA reductase inhibitors and fibrates (like gemfibrozil, fenofibrates) should be generally avoided (see section 4.4 ‘Skeletal muscle effects’ and see section 4.5).

Dosage in patients taking ciclosporin, clarithromycin, itraconazole or certain protease inhibitors

In patients using ciclosporin or the HIV protease inhibitors (tipranavir plus ritonavir) or the hepatitis C protease inhibitor (telaprevir), treatment with COLASTIN-L should be avoided. In patients taking clarithromycin, itraconazole, or in patients taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, therapy with COLASTIN-L should be limited to 20 mg, and appropriate clinical assessment is recommended to ensure that the lowest dose necessary of atorvastatin is employed. In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, therapy with COLASTIN-L should be limited to 40 mg, and appropriate clinical assessment is recommended ensure that the lowest dose necessary of atorvastatin is employed (see section 4.4 'Skeletal muscle effects' and see section 4.5).

4.3 Contraindications

COLASTIN-L is contraindicated in patients:

- With hypersensitivity to the components of this medicinal product,
- 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 childbearing potential not using appropriate contraceptive measures.

4.4 Special warnings and precautions for use

Hepatic effects

As with other lipid-lowering agents of the same class, moderate (> 3 x upper limit of normal [ULN]) elevations of serum transaminases have been reported following therapy with atorvastatin. In this case, a dose reduction or discontinuation of atorvastatin therapy is recommended. Liver functions were monitored in both pre-marketing as well as post-marketing clinical studies of atorvastatin at doses of 10, 20, 40 and 80 mg. Persistent increases in serum transaminases (> 3 x ULN on two or more occasions) occurred in 0.7% of patients who received atorvastatin. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg respectively. Increases were generally not associated with jaundice or other clinical signs or symptoms. When the dosage of atorvastatin was reduced, or drug treatment interrupted or discontinued, transaminase levels returned to pre-treatment levels. Most patients continued treatment on a reduced dose of atorvastatin without sequelae.

Liver function tests should be performed before the initiation of treatment with COLASTIN-L and periodically thereafter when clinically necessary (if signs or symptoms of liver damage occur). There have been rare post-marketing reports of fatal and non-fatal liver failure in patients taking statins, including atorvastatin. If clinically symptomatic liver damage and/or hyperbilirubinemia or jaundice occur during treatment with COLASTIN-L, the treatment should be stopped immediately. If an alternate etiology is not found, COLASTIN-L treatment should not be restarted.

All patients treated with COLASTIN-L should be advised to promptly report any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice.

Atorvastatin can cause an elevation in transaminases (see section 4.8).

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see section 4.3).

Skeletal muscle effects
As with other drugs in this class, rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported. A history of renal impairment may be a risk factor for developing rhabdomyolysis. Such patients should be monitored closely for effects on skeletal muscle.

Like other statins, atorvastatin rarely causes myopathy, defined by muscle aches and muscle weakness associated with an increase in CPK levels more than 10 times the upper limit of normal (ULN). Concomitant use of high doses of atorvastatin with certain drugs, such as cyclosporine and potent inhibitors of CYP3A4 (e.g. clarithromycin, itraconazole, and HIV protease inhibitors), increases the risk of myopathy/rhabdomyolysis.

Immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, has been rarely reported with statin use. IMNM is characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if they are accompanied by malaise or fever, or if muscle signs and symptoms persist after discontinuing COLASTIN-L. COLASTIN-L therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives (e.g. gemfibrozil, fenofibrate), erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, combinations of HIV protease inhibitors, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, niacin, colchicine or azole antifungals. Physicians considering combined therapy with COLASTIN-L and fibric acid derivatives (such as gemfibrozil, fenofibrate), erythromycin, clarithromycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, and fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with the afore-mentioned drugs (see section 4.5). Periodic creatine phosphokinase determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

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

Drug interactions associated with increased risk of myopathy/rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine, HIV protease inhibitors (tipranavir plus ritonavir), hepatitis C protease inhibitor (telaprevir)	Avoid atorvastatin usage
HIV protease inhibitor (lopinavir plus ritonavir)	Use with caution and lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir plus ritonavir*, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir)	Do not exceed 20 mg atorvastatin daily
HIV protease inhibitor (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg atorvastatin daily
*Use with caution and with the lowest dose necessary	

Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection; hypotension; major surgery; trauma; severe metabolic, endocrine and electrolyte disorders; and uncontrolled seizures).

<u>Diabetes mellitus and endocrine function effects</u>
As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with COLASTIN-L. In patients with risk factors for diabetes, an increase in the incidence of diabetes has been reported with COLASTIN-L.

However, given the benefit of HMG-CoA reductase inhibitors in reducing the frequency of major cardiovascular events, the overall benefit-harm balance appears to be distinctly favorable, and therefore, there should be no reason to discontinue statin therapy. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30 mg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically.

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Hemorrhagic stroke
A post-hoc analysis of a clinical study in 4,731 patients without coronary heart disease (CHD) who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and were initiated on atorvastatin 80 mg, revealed a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared to placebo (55 atorvastatin vs. 33 placebo). Patients with hemorrhagic stroke on entry appeared to be at increased risk for recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo). However, in patients treated with atorvastatin 80 mg, there were fewer strokes of any type (265 atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo) (see section 5.1 'Recurrent stroke').

Warnings for patients
Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if they are accompanied by malaise or fever.

Pediatric use
Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration. Patients treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo. The most common adverse experiences, regardless of causality assessment, were infections. Doses greater than 20 mg have not been studied in this patient population. In this limited controlled study, there was no significant effect on growth or sexual maturation in boys or on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on atorvastatin therapy (see sections 4.3, 4.4 and 4.6). Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Information on the safety of growth and development in the pediatric population is not sufficient.

Geriatric use
Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (aged ≥ 65 years) than in young adults. The LDL-K reduction was similar to that seen in young patient populations receiving equal doses of atorvastatin (see section 5.2).

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 dyspnea, 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.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.
This medicinal product contains less than 1 mmol (23 mg) sodium per dose. No side effects are expected due to sodium at this dose.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant administration of cyclosporine, fibric acid derivatives (such as gemfibrozil, fenofibrate), niacin or cytochrome P450 3A4 inhibitors (such as erythromycin, clarithromycin [see below] and azole antifungals) with HMG-CoA inhibitors may lead to increased risk of myopathy (see section 4.4 'Skeletal muscle effects').

Daily initial dose of atorvastatin should be 10 mg in patients receiving medication that increases the plasma concentration of atorvastatin. If taking clarithromycin and itraconazole, a lower maximum atorvastatin dose should be used.

Cytochrome P450 3A4 inhibitors
Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant administration of inhibitors of P450 3A4 may lead to increased plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on cytochrome P450 3A4.

Erythromycin/clarithromycin
The combination of atorvastatin with erythromycin (500 mg, 4 times daily) or clarithromycin (500 mg twice daily), known inhibitors of cytochrome P450 3A4, has been associated with high plasma atorvastatin concentrations (see section 4.4 'Skeletal muscle effects'). If clarithromycin should be co-administered with atorvastatin, the maintenance dose should not exceed 20 mg daily.

Protease inhibitors
Atorvastatin AUC was significantly increased with several combinations of HIV protease inhibitors, as well as with the hepatitis C protease inhibitor telaprevir, compared to that of atorvastatin alone. Therefore, in patients taking the HIV protease inhibitor, tipranavir plus ritonavir, or the hepatitis C protease inhibitor telaprevir, concomitant use of atorvastatin should be avoided. In patients taking the HIV protease inhibitor lopinavir plus ritonavir, caution should be used when prescribing COLASTIN-L and the lowest dose necessary should be used. In patients taking the HIV protease inhibitors saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir, the dose of COLASTIN-L should not exceed 20 mg and should be used with caution (see section 4.2 and see section 4.4 'Skeletal muscle effects'). In patients taking the HIV protease inhibitor nelfinavir or the hepatitis C protease inhibitor boceprevir, the dose of COLASTIN-L should not exceed 40 mg and close clinical monitoring is recommended.

Diltiazem hydrochloride
Concomitant administration of atorvastatin (40 mg) and diltiazem (240 mg) resulted in increased atorvastatin plasma concentrations.

Cimetidine
Interaction studies with cimetidine have been conducted and no clinically significant interactions have been observed.

Itraconazole
Concomitant administration of atorvastatin (20 to 40 mg) and itraconazole (200 mg) was associated with an increase in atorvastatin AUC. When itraconazole is to be administered concomitantly with atorvastatin, the maintenance dose of atorvastatin should not exceed 40 mg daily.

Grapefruit Juice
Some substances in grapefruit juice inhibit CYP 3A4 and lead to elevated plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (>1.2 liters per day).

Inducers of cytochrome P450 3A4
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin (cytochrome P450 3A4 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.

Antacids
Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminum hydroxide decreased plasma concentrations of atorvastatin by approximately 35%, with no change in the LDL-C reduction ratio.

Antipyrine
Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Azithromycin
Co-administration of atorvastatin 10 mg once daily and azithromycin 500 mg once daily did not alter the plasma concentrations of atorvastatin.

Oral contraceptives
Co-administration of atorvastatin with an oral contraceptive containing norethindrone and ethinyl estradiol increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin.

Warfarin
Atorvastatin had no clinically significant effect on prothrombin time when administered to

patients receiving chronic warfarin treatment. However, if patients on warfarin need to use COLASTIN-L, they should closely be monitored.

Amlodipine
In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin which was not clinically meaningful.

Colchicine
Cases of myopathy, including rhabdomyolysis, have been reported with atorvastatin co administered with colchicine, and caution should therefore be exercised when prescribing atorvastatin with colchicine.

Transport protein inhibitors
Atorvastatin and its metabolites are substrates of the OATP1B1 transporter. OATP1B1 inhibitors (e.g. cyclosporine) increase the bioavailability of atorvastatin. Concomitant administration of atorvastatin 10 mg and cyclosporine 5.2 mg/kg/day resulted in a 7.7-fold increase in exposure to atorvastatin.

The co-administration of atorvastatin with cyclosporine should be avoided (see section 4.4 ‘Skeletal muscle effects’).

Gemfibrozil
Due to an increased risk of myopathy/rhabdomyolysis when HMG-CoA reductase inhibitors are co-administered with gemfibrozil, concomitant administration of COLASTIN-L with gemfibrozil should be avoided.

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 were lower (approximately 25%) when colestipol and atorvastatin were co-administered. However, LDL-C reduction was greater when atorvastatin and colestipol were co-administered than when either drug was given alone.

Fusidic acid
Although interaction studies with atorvastatin and fusidic acid have not been conducted, there have been reports of severe muscle problems, such as rhabdomyolysis, with this combination in post-marketing experience. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased by approximately 20% following administration of 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.

Other fibrates
Because it is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of other fibrates, COLASTIN-L should be administered with caution when used concomitantly with other fibrates.

Niacin
The risk of skeletal muscle effects may be enhanced when COLASTIN-L is used in combination with niacin; a reduction in COLASTIN-L dosage should be considered in this setting.

Other concomitant therapy
In clinical studies, atorvastatin was used concomitantly with antihypertensive agents and estrogen replacement therapy without evidence of clinically significant adverse interactions. Interaction studies with specific agents have not been conducted.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is X.

Women of childbearing potential / Birth Control (Contraception)
Women of childbearing potential should use appropriate contraceptive measures (see section 4.3). Atorvastatin should be used in women of childbearing age only in those who are deemed highly unlikely to become pregnant and when informed of the potential hazards to the fetus.

Pregnancy
Atorvastatin is contraindicated during pregnancy.

Lactation
Atorvastatin is contraindicated during lactation. It is unknown whether this medicine is excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, women using atorvastatin should not breast-feed (see section 4.3).

Reproduction ability / Fertility
See section 5.3.

4.7 Effects on ability to drive and use machines

COLASTIN-L has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Atorvastatin is generally well tolerated. Adverse reactions were mostly mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 atorvastatin vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the ones on placebo.
Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for COLASTIN-L.
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 : Hyperglycemia
Uncommon : Hypoglycemia, weight gain, anorexia

Psychiatric disorders
Uncommon : Nightmare, insomnia

Nervous system disorders
Common : Headache
Uncommon : Dizziness, paresthesia, 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, diarrhea
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 edema, 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, tendinopathy, sometimes complicated by rupture

Reproductive system and breast disorders
Uncommon : Impotence
Very rare : Gynecomastia

General disorders and administration site conditions
Uncommon : Malaise, asthenia, chest pain, peripheral edema, 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 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).

Pediatric Population
The clinical safety database includes safety data for 249 pediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the range of 10 to 17.

Nervous system disorders
Common : Headache

Gastrointestinal disorders
Common : Abdominal pain

Investigations
Common : Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the pediatric population.

The following adverse events have been reported with some statins:

- Sleep disturbances including insomnia and having nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Isolated 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 > 30kg/m^2 raised triglycerides, history of hypertension).

There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive problems have been reported for all statins. The reported symptoms are generally not serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median of 3 weeks).

Immune-mediated necrotizing myopathy associated with the use of statin has rarely been reported (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose
Specific treatment is not available for COLASTIN-L overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted, as required. Liver function tests should be performed and serum CPK levels should be monitored. Due to extensive atorvastatin binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Cardiovascular drugs, serum 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 (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. Atorvastatin reduces total-C, LDL-C and apo B in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemia; it also reduces VLDL-C and triglycerides (TG) and produces variable increases in HDL-C.

Triglycerides and cholesterol in the liver are incorporated into VLDL (very low-density lipoprotein) and released into the plasma for delivery to peripheral tissues. LDL (low-density lipoprotein) is formed from VLDL and is catabolized primarily through the high-affinity LDL receptor. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also promote atherosclerosis.

Elevated plasma triglycerides are frequently found in a triad with low HDL cholesterol levels and small LDL particles, as well as in association with non-lipid metabolic risk factors for coronary heart disease (CDH). As such, total plasma triglycerides has not consistently been shown to be an independent risk factor for coronary heart disease.

Atorvastatin lowers plasma cholesterol and LDL levels 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 reduces total cholesterol, LDL cholesterol, VLDL cholesterol, apo B, triglycerides, but it increases HDL cholesterol. Atorvastatin reduces intermediate density lipoprotein cholesterol (IDL-C) in patients with dysbetalipoproteinemia.

In a dose response study, atorvastatin (10 to 80 mg) has been shown to reduce concentrations of total cholesterol (30-46%), LDL cholesterol (41-61%), apo B (34-50%), and triglycerides (14-33%). These results are consistent in patients with heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and combined hypercholesterolemia, including patients with noninsulin-dependent diabetes mellitus.

In a controlled 24 trials of atorvastatin 10-80 mg for patients with Fredrickson type IIa and IIb hyperlipoproteinemia, analysis of pooled data demonstrated consistently significant reductions from baseline in total cholesterol, LDL cholesterol, triglyceride levels, and total-C/HDL-C and LDL-C/HDL-C ratios. Additionally, atorvastatin (10 to 80 mg) increased HDL-C by an average of 5.1-8.7% in a non-dose-related manner.

Atorvastatin and some of its metabolites are pharmacologically active in humans. The primary site of action of atorvastatin is the liver, which is the principal site of cholesterol synthesis and LDL clearance. LDL-C reduction correlates better with drug dose than it does with systemic drug concentration. Individualization of drug dosage should be based on therapeutic response (see section 4.2).

Prevention of Cardiovascular Disease

In the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), with no previous myocardial infarction or treatment for angina and with total cholesterol levels < 251 mg/dL. Additionally, all patients had at least 3 of the following cardiovascular risk factors: male gender, age > 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. In this double-blind placebo-controlled study, patients were treated with antihypertensive therapy (goal blood pressure < 140/90 mmHg for non-diabetic patients, < 130/80 mmHg for diabetic patients) and allocated to either atorvastatin 10 mg daily (n=5168) or placebo (n=5137). Interim analysis of this trial, with adequate blood pressure control was achieved in both treatment arms, showed a decline in cardiovascular event risks exceeding threshold for statistical significance in the atorvastatin arm compared to placebo arm; thus, the trial was terminated earlier (3.3 years) than planned (5 years).

In the ASCOT trial, atorvastatin significantly reduced the incidence of the following events:

Event	Risk reduction (%)	Number of events (atorvastatin vs. placebo)	P-value
Coronary events (fatal CDH + non-fatal MI)	%36	100 vs. 154	0.0005
Total cardiovascular events and revascularization procedures	%20	389 vs. 483	0.0008
Total coronary events	%29	178 vs. 247	0.0006
Fatal and non-fatal stroke*	%26	89 vs. 119	0.0332

* Although the reduction of fatal and non-fatal strokes did not reach a predefined significance level (p=0.01), a favorable trend was observed with a 26% relative risk reduction.

The risk reduction is consistent regardless of age, smoking, obesity and renal dysfunction.

There was no significant difference between groups in terms of total mortality (p=0.17) and cardiovascular mortality (p=0.51).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and non-fatal cardiovascular disease (CVD) was assessed in 2838 patients with Type 2 diabetes 40 to 75 years of age, without prior history of CVD and with LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. Additionally, all patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria. In this randomized, double blind, multicenter, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years. As the effect of atorvastatin treatment on the primary endpoint reached the predefined stopping rules for efficacy, CARDS was terminated 2 years earlier than anticipated.

In the CARDS trial, absolute and relative risk reduction effect of atorvastatin was as follows:

Event	Relative risk reduction (%)	Number of events (atorvastatin vs. placebo)	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	0.0010
MI (fatal and non-fatal AMI, silent MI)	%42	38 vs. 64	0.0070
Strokes (fatal and non-fatal)	%48	21 vs. 39	0.0163

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 favorable trend for relative risk reduction was observed regarding the mortality rate of 27% (82 deaths in the placebo group vs. 61 deaths in the treatment arm, [p=0.0592]).

The overall incidence of adverse events or serious adverse events was similar between the treatment groups.

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In this study, no atherosclerosis progression was seen in the atorvastatin arm (n=253). The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group (n=253) 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).

In the atorvastatin group, LDL-C was reduced to a mean of 78.9 mg/dL ±30 from baseline 150 mg/dL ±28, and in the pravastatin group, LDL-C was reduced to a mean of 110 mg/dL ±26 from baseline 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 = not significant). 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).

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

Prevention of 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 4731 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 to 92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL. The mean LDL-C was 73 mg/dL during treatment with atorvastatin and 129 mg/dL 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% (hazard ratio [HR] 0.85; 95% CI 0.72-1.00; p=0.05, or HR 0.84; 95% CI 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. Atorvastatin 80 mg significantly reduced the risk of major coronary events (HR 0.67; 95% CI 0.51-0.89; p=0.006), any CHD event (HR 0.60; 95% CI 0.48-0.74; p<0.001), and revascularization procedures (HR 0.57; 95% CI 0.44-0.74; p<0.001).

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo. The incidence of fatal hemorrhagic stroke was similar between the groups (17 atorvastatin vs. 18 placebo). Reduction in the risk of cardiovascular events with atorvastatin 80 mg was demonstrated in all patient groups except in patients who entered the study with a hemorrhagic stroke and had a recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo).

In patients treated with atorvastatin 80 mg, there were fewer strokes of any type (265

atorvastatin vs. 311 placebo) and fewer CHD events (123 atorvastatin vs. 204 placebo). Overall mortality was similar across treatment groups (216 atorvastatin vs. 211 placebo). The overall incidence of adverse events was similar between the treatment groups.

Secondary Prevention of Cardiovascular Events

In the Treating to New Targets Study (TNT), the effect of atorvastatin 80 mg/day vs. atorvastatin 10 mg/day on the reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥65 years) with clinically evident coronary heart disease who had achieved a target LDL-C level <130 mg/dL after completing an 8-week, open-label, run-in period with atorvastatin 10 mg/day. Subjects were randomly assigned to either 10 mg/day or 80 mg/day of atorvastatin and followed for a median duration of 4.9 years. The mean LDL-C, TC, TG, non-HDL-C and HDL-C levels at 12 weeks were 73 mg/dL, 145 mg/dL, 128 mg/dL, 98 mg/dL and 47 mg/dL, respectively, during treatment with 80 mg of atorvastatin, and 99 mg/dL, 177 mg/dL, 152 mg/dL, 129 mg/dL and 48 mg/dL, respectively, during treatment with 10 mg of atorvastatin.

In the TNT study, the primary endpoint was time to major cardiovascular event (death from CHD, non-fatal myocardial infarction, resuscitated arrest, fatal or non-fatal stroke). There were fewer major cardiovascular events (MCVE) in the atorvastatin 80 mg/day arm compared to the atorvastatin 10 mg/day arm (434 events in the 80 mg/day group vs. 548 events in the 10 mg/day group) and a relative risk reduction of 22% in MCVE was achieved with atorvastatin 80 mg/day treatment (p=0.0002).

In the TNT study, atorvastatin 80 mg/day significantly reduced the risk of the following:

Significant Endpoint	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (%95 CI)
PRIMARY ENDPOINT*	n	(%)	n	(%)	
First major cardiovascular endpoint	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the Primary Endpoint					
Non-fatal, non-procedure related MI	308	(6.2)	243	(4.9)	0.78 (0.66, 0.93)
Stroke (fatal and non-fatal)	155	(3.1)	117	(2.3)	0.75 (0.59, 0.96)
SECONDARY ENDPOINTS**					
First CHF with hospitalization	164	(3.3)	122	(2.4)	0.74 (0.59, 0.94)
First CABG or other coronary revascularization procedure[b]	904	(18.1)	667	(13.4)	0.72 (0.65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)

a Atorvastatin 80 mg: atorvastatin 10 mg.

b Component of other secondary endpoints.

* MCVE=death due to CHD, non-fatal MI, resuscitated cardiac arrest, and fatal and non-fatal stroke.

** Secondary endpoints not included in primary endpoint.

HR=hazard ratio; CI=confidence interval; MI=myocardial infarction; CHF=congestive heart failure; CABG=coronary artery bypass graft

Confidence intervals for the secondary endpoints were not adjusted for multiple comparisons.

There was no significant difference between the treatment groups for all-cause mortality: 282 (5.6%) in the atorvastatin 10 mg/day group vs. 284 (5.7%) in the atorvastatin 80 mg/day group. The proportions of subjects who experienced cardiovascular death, including the components of CHD death and fatal stroke were numerically smaller in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group. The proportions of subjects who experienced non-cardiovascular death were numerically larger in the atorvastatin 80 mg group than in the atorvastatin 10 mg treatment group.

The effects of atorvastatin on ischemic events and total mortality were studied in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study (MIRACL). This multicenter, randomized, double blind, placebo-controlled study followed 3086 patients with acute coronary syndromes (unstable angina or non-Q wave MI). Patients were randomized to atorvastatin 80 mg daily or placebo for a median duration of 16 weeks. The final LDL-C, total-C, HDL-C and TG levels were 72 mg/dL, 147 mg/dL, 48 mg/dL, and 139 mg/dL in the atorvastatin group, respectively, and 135 mg/dL, 217 mg/dL, 46 mg/dL, and 187 mg/dL, respectively, in the placebo group. Atorvastatin significantly reduced the risk of ischemic events and death by 16%. The risk of experiencing re-hospitalization for angina pectoris with documented evidence of myocardial ischemia was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to a similar extent across the range of baseline LDL-C. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients with non-Q-wave MI and unstable angina, as well as in males and females and in patients ≤65 years of age and >65 years of age.

In the Incremental Decrease in Endpoints Through Aggressive Lipid Lowering Study (IDEAL), treatment with atorvastatin 80 mg/day was compared to treatment with simvastatin 20 mg/day to 40 mg/day in 8888 subjects (up to 80 years of age) with a history of CHD to assess whether reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) with an average age of 61.7 years and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this prospective, randomized, open-label, blinded endpoint trial, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL and non-HDL cholesterol levels at Week 12 were 78 mg/dL, 145 mg/dL, 115 mg/dL, 45 mg/dL and 100 mg/dL, respectively, during treatment with 80 mg of atorvastatin, and 105 mg/dL, 179 mg/dL, 142 mg/dL, 47 mg/dL and 132 mg/dL, respectively, during treatment with 20-40 mg/day of simvastatin.

There was no significant difference between the treatment groups for the primary endpoint, the rate of first major coronary event (fatal CHD, non-fatal MI and resuscitated cardiac arrest): 411 (9.3%) in the atorvastatin 80 mg/day group vs. 463 (10.4%) in the simvastatin 20-40 mg/day group, HR 0.89; 95% CI 0.78 - 1.01; p=0.07. There were no significant differences between the treatment groups for all-cause mortality: 366 (8.2%) in the atorvastatin 80 mg group vs. 374 (8.4%) in the simvastatin 20 mg to 40 mg group. The proportions of subjects who experienced CV or non-CV death were similar for both treatment arms.

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-controlled study followed by an open-label phase, 187 boys and post-menarchal girls 10 to 17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolemia were randomized to atorvastatin

(n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥190 mg/dL or 2) a baseline LDL-C level ≥160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5–385.0 mg/dL) in the atorvastatin group compared to 230.0 mg/dL (range: 160.0–324.5 mg/dL) in the placebo group. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if the LDL-C level was >130 mg/dL. The number of atorvastatin-treated patients who required up-titration to 20 mg after Week 4 during the double-blind phase was 80 (57.1 %).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase.

Lipid Lowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Change from Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipoprotein B
Placebo	47	-1.5	-0.4	-1.9	1.0	0.7
Atorvastatin	140	-31.4	-39.6	2.8	-12.0	-34.0

The mean achieved LDL-C value was 130.7 mg/dL (range: 70.0–242.0 mg/dL) in the atorvastatin group compared to 228.5 mg/dL (range: 152.0–385.0 mg/dL) in the placebo group during the 26-week double-blind phase.

In this limited controlled study, there was no detectable effect on the menstrual cycle duration of girls or on the sexual maturation and growth of boys. Atorvastatin has not been studied in controlled clinical trials in pre-puberty patients or in children under 10 years of age. The safety and efficacy of doses above 20 mg have not been tested in controlled studies in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality during adulthood has not been determined.

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption and plasma atorvastatin concentrations increase in proportion to atorvastatin dose. Atorvastatin tablets have 95% to 99% bioavailability compared to solutions. The absolute bioavailability of atorvastatin is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to pre-systemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whether atorvastatin is given with or without food. Plasma atorvastatin concentrations are lower (approximately 30% for C_{max} and AUC) following evening drug administration compared with morning. However, LDL-C reduction

is the same regardless of the time of day of drug administration (see section 4.2).

Distribution
Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥ 98% bound to plasma proteins. A blood/plasma ratio of approximately 0.25 indicates poor drug penetration into red blood cells.

Biotransformation
Atorvastatin is extensively metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *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. *In vitro* studies suggest the importance of atorvastatin metabolism by hepatic cytochrome P450 3A4, consistent with increased plasma concentrations of atorvastatin in humans following co-administration with erythromycin, a known inhibitor of this isozyme. *In vitro* studies also indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Atorvastatin co-administration did not produce a clinically significant effect in plasma concentrations of terfenadine, a compound predominantly metabolized by cytochrome P450 3A4; therefore, it is unlikely that atorvastatin will significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see section 4.5). In animals, the ortho-hydroxy metabolite undergoes further glucuronidation.

Elimination
Atorvastatin and its metabolites are eliminated primarily in bile following hepatic and/or extrahepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites. Less than 2% of a dose of atorvastatin is recovered in urine following oral administration.

Special populations
Elderly
Plasma concentrations of atorvastatin are higher (approximately 40% for C_{max} and 30% for AUC) in healthy elderly subjects (aged ≥ 65 years) than in young adults. The ACCESS study specifically evaluated elderly patients with respect to reaching their NCEP treatment goals. The study included 1087 patients under 65 years of age, 815 patients over 65 years of age, and 185 patients over 75 years of age. No differences in safety, efficacy or lipid treatment goal attainment were observed between elderly patients and the overall population.

Pediatric population
Pharmacokinetic data in the pediatric population are not available.

Gender
Plasma concentrations of atorvastatin in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. However, there were no clinically significant differences in lipid effects between men and women.

Renal impairment
Renal disease has no influence on the plasma atorvastatin concentrations or LDL-C reduction;

thus, dose adjustment in patients with renal dysfunction is not necessary (see section 4.2).

Hemodialysis
While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin since the drug is extensively bound to plasma proteins.

Hepatic Impairment
Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (see section 4.3).

SLCO1B1 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.

Drug interactions
The effect of co-administered drugs on the pharmacokinetics of atorvastatin as well as the effect of atorvastatin on the pharmacokinetics of co-administered drugs are given in the following table (see sections 4.4 and 4.5).

Effect of co-administered drugs on the pharmacokinetics of atorvastatin

Co-administered drug and dosing regimen	**Atorvastatin**		
	Dose (mg)	**Change in AUC[&]**	**Change in C_{max}[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	Once a day 10 mg per day for 28 days	↑ 8.7 fold	↑ 10.7 fold
[#]Tipranavir 500 mg twice a day / ritonavir 200 mg twice a day, 7 days	Single dose 10 mg	↑ 9.4 fold	↑ 8.6 fold
[#]Telaprevir 750 mg q&h, 10 days	Single dose 20 mg	↑ 7.88 fold	↑ 10.6 fold
[#‡]Saquinavir 400 mg twice a day / ritonavir 400 mg twice a day, 15 days	40 mg once a day for 4 days	↑ 3.9 fold	↑ 4.3 fold
[#]Clarithromycin 500 mg twice a day, 9 days	80 mg once a day for 8 days	↑ 4.4 fold	↑ 5.4 fold
[#]Darunavir 300 mg twice a day / ritonavir 100 mg twice a day, 9 days	10 mg once a day for 4 days	↑ 3.4 fold	↑ 2.25 fold
[#]Itraconazole 200 mg once a day, 4 days	Single dose 40 mg	↑ 3.3 fold	↑ 20%
[#]Fosamprenavir 700 mg twice a day / ritonavir 100 mg twice a day, 14 days	10 mg once a day for 4 days	↑ 2.53 fold	↑ 2.84 fold
[#]Fosamprenavir 1400 mg twice a day, 14 days	10 mg once a day for 4 days	↑ 2.3 fold	↑ 4.04 fold
[#]Nelfinavir 1250 mg twice a day, 14 days	10 mg once a day	↑ 74%	↑ 2.2 fold

	for 28 days		
#Grapefruit Juice 240 mL, once a day*	Single dose 40 mg	↑ 37%	↑ 16%
Diltiazem 240 mg once a day, 28 days	Single dose 40 mg	↑ 51%	No change
Erythromycin 500 mg four times a day, 7 days	Single dose 10 mg	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	Single dose 80 mg	↑ 15%	↓ 12%
Cimetidine 300 mg once a day, 4 weeks	10 mg once a day for 2 weeks	↑ Less than 1%	↓ 11%
Colestipol 10 mg twice a day, 28 weeks	40 mg once a day for 28 weeks	Not determined	↓ 26%**
Aluminum hydroxide and magnesium hydroxide combination 30 mL once a day, 17 days	10 mg once a day for 15 days	↓ 33%	↓ 34%
Efavirenz 600 mg once a day, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
#Rifampin 600 mg once a day, 7 days (co-administered)†	Single dose 40 mg	↓ 30%	↑ 2.7 fold
#Rifampin 600 mg once a day, 5 days (in separate doses)†	Single dose 40 mg	↓ 80%	↓ 40%
#Gemfibrozil 600 mg twice a day, 7 days	Single dose 40 mg	↑ 35%	↓ Less than 1%
Fenofibrate 160 mg once a day, 7 days	Single dose 40 mg	↑ 3%	↑ 2%
Boceprevir 800 mg three times a day, 7 days	Single dose 40 mg	↑ 2.30 fold	↑ 2.66 fold

& 'fold' change = rate change [(I-B)/B], I = pharmacokinetic value during the interaction phase, B = pharmacokinetic value during baseline phase; % change = % rate change

See sections 4.4 and 4.5 for clinical significance.

* Greater increases in the area under the curve (AUC) (up to 1.5 fold) and/or C_{max} (up to 71%) have been reported with excessive grapefruit consumption (≥ 750 mL - 1.2 liters per day).

** Single sample taken 8 - 16 h post dose.

† Due to the dual interaction mechanism of rifampin, 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 dose of saquinavir and ritonavir dose in this study is not the clinically used dose. Therefore, caution should be applied and the lowest dose necessary should be used.

Effect of atorvastatin on the pharmacokinetics of co-administered drugs

Atorvastatin	**Co-administered drug and dosing regimen**		
	Drug / Dose (mg)	**Change in AUC&**	**Change in C_{max}&**
80 mg once a day for 15 days	Antipyrine, single dose 600 mg	↑ 3% fold	↓ 11% fold
80 mg once a day for 14 days	#Digoxin 0.25 mg once a day, 20 days	↑ 15% fold	↑ 20% fold
40 mg once a day for 22 days	Oral contraceptive once a day, 2 months - norethindrone 1	↑ 28% fold ↑ 19% fold	↑ 23% fold ↑ 30% fold

	mg - ethinyl estradiol 35 mcg		
Single dose 10 mg	Tipranavir 500 mg twice a day / ritonavir 200 mg twice a day, 7 days	No change	No change
10 mg once a day for 4 days	Fosamprenavir 1400 mg twice a day, 14 days	↓ 27%	↓ 18%
10 mg once a day for 4 days	Fosamprenavir 700 mg twice a day / ritonavir 100 mg twice a day, 14 days	No change	No change

& % change = % rate change [(I-B)/B], I = pharmacokinetic value during the interaction phase, B = pharmacokinetic value during baseline phase

See section 4.5 for clinical significance.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$. All chemically similar drugs in this class induced tumors in both mice and rats at 12- to 125-fold of the highest recommended clinical dose on a mg/kg body-weight basis.

In vitro, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation (in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, in the *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells, and in the chromosomal aberration assay in *in vitro* Chinese hamster lung cells). Atorvastatin was negative in the *in vivo* mouse micronucleus test.

In animal studies, atorvastatin had no adverse effect on male or female fertility at doses up to 175 and 225 mg/kg/day. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg body-weight basis. Atorvastatin did not cause any adverse effects on sperm or semen parameters, or in reproductive organ histopathology in dogs given doses of 10, 40 or 120 mg/kg for 2 years.

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

Lactose monohydrate
Calcium carbonate
Microcrystalline cellulose PH 101
Microcrystalline cellulose PH 102
Croscarmellose sodium
Hydroxypropyl cellulose-L
Polysorbate 80
Magnesium stearate
Film coating agents:

- Opadry YS-1-7040 White (Hydroxypropyl methyl cellulose, Polyethylene glycol, Titanium dioxide, Talc)
- Simethicone emulsion

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at room temperature below 25°C.

6.5 Nature and contents of packaging

Alu-alu blister composed of aluminum foil on one side and formable aluminum foil (Formpack) on the other side.
Each cardboard box contains 30 or 90 tablets.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – ISTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

209/83

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 24.11.2006
Date of last renewal :

10. DATE OF REVISION OF THE TEXT