SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
COLASTIN-L 80 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Equivalent to 80 mg Atorvastatin
Atorvastatin calcium trihydrate ..... 86.602 mg

Excipient(s):
Lactose monohydrate ..... 332.000 mg
Croscarmellose sodium ..... 76.000 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet.
White film-coated, oblong tablets with a homogeneous appearance, scored on one side and embossed with "80" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia
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 increased 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
Prevention of cardiovascular events in adult patients estimated to have a high risk for a first cardiovascular event, 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 starting dose 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, 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 use 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 disease has no influence on the plasma concentrations and LDL-C reduction of atorvastatin. Thus, dose adjustment in patients with renal dysfunction is not necessary (see sections 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):
The recommended starting dose of COLASTIN-L is 10 mg daily; the maximum recommended dose is 20 mg daily (doses above 20 mg and combined therapy have not been studied in this patient population). The dose should be individualized according to the recommended treatment goal (see section 5). Dose adjustments should be made at least every 4 weeks.

Geriatric population:
No difference in efficacy and safety was observed between elderly patients and general population at recommended doses (see section 4.4).

Concomitant use with 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 4.5).

Dosage in patients using ciclosporin, clarithromycin, itraconazole or certain protease inhibitors
In patients using ciclosporin or HIV protease inhibitors (tipranavir and 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 clinical assessment is recommended ensure that the lowest dose necessary of atorvastatin is employed (see section 4.4 Skeletal Muscle Effects and 4.5).

4.3 Contraindications

COLASTIN-L is contraindicated in following patients:

- With hypersensitivity to any component of this medicine
- 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

4.4 Special warnings and precautions for use

Liver effects:
As with other lipid-lowering agents in the same class, moderate elevations in serum transaminases (>3 times the upper limit of normal (ULN)) have been reported following atorvastatin therapy. In these cases, dose reduction or discontinuation of atorvastatin is recommended. Liver function was monitored in both pre-marketing and post-marketing clinical studies with atorvastatin 10, 20, 40, and 80 mg doses. Sustained elevations in serum transaminases (>3 times the upper limit of normal on two or more occasions) were observed in 0.7% of patients receiving atorvastatin. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for the 10, 20, 40, and 80 mg doses, respectively. These elevations were generally not accompanied by jaundice or other clinical signs and symptoms. Transaminase levels returned to pretreatment values when the atorvastatin dose was reduced, interrupted, or discontinued. Most patients were able to continue treatment with lower doses of atorvastatin without sequelae.

It is recommended that liver enzyme tests be performed before initiating treatment with COLASTIN-L and repeated as clinically indicated (if signs or symptoms of liver injury occur). Rare post-marketing reports of fatal and non-fatal liver failure have been reported in patients taking statins, including atorvastatin. If clinically symptomatic liver injury and/or hyperbilirubinemia or jaundice occur during treatment with COLASTIN-L, treatment should be stopped immediately. Unless an alternative etiology is found, COLASTIN-L treatment should not be restarted.

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

Atorvastatin may cause elevations in transaminase levels (see section 4.8).

Atorvastatin should be used with caution in patients who consume significant amounts of alcohol and/or have a history of liver disease. Atorvastatin is contraindicated in patients with active liver disease or unexplained persistent transaminase elevations (see section 4.3).

Skeletal muscle effects:
As with other drugs in this class, rhabdomyolysis has been reported in rare cases with acute renal failure secondary to myoglobinuria. A history of renal impairment may be a risk factor for the

development of rhabdomyolysis. Such patients should be closely monitored for their effects on skeletal muscle.

Like other statins, atovastatin rarely causes myopathy, characterized by muscle aches and weakness associated with elevations in CPK levels greater than 10 times the upper limit of normal (ULN). The risk of myopathy/rhabdomyolysis is increased with the concomitant use of high doses of atorvastatin with certain drugs, such as cyclosporine and strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, and HIV protease inhibitors).

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

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

The risk of myopathy is increased when drugs of this class are used concomitantly with cyclosporine, fibric acid derivatives (e.g., gemfibrozil, fenofibrate), erythromycin, clarithromycin, the hepatitis C protease inhibitor telaprevir, HIV protease inhibitor combinations including saquinavir plus ritonavir, lopinavir plus ritonavir, tipranavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, fosamprenavir plus ritonavir, niacin, colchicine, or azole antifungals. Physicians considering combined use of COLASTIN-L with fibric acid derivatives (e.g., gemfibrozil, fenofibrate), erythromycin, clarithromycin, saquinavir plus ritonavir, lopinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir or fosamprenavir plus ritonavir, azole antifungals, or lipid-modifying doses of niacin should consider the potential benefits and risks and carefully monitor patients for signs and symptoms of muscle pain, tightness, or weakness during the dose titration period for either drug, particularly during the initial months of treatment. Consider lower starting and maintenance doses of atorvastatin if these products are used concomitantly with atorvastatin (see Section 4.5). In this case, periodic creatine phosphokinase measurements should be considered; however, there is no guarantee that such monitoring will prevent the development of severe myopathy.

Before treatment in patients at risk of rhabdomyolysis:
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

- Situations where an increase in plasma levels of CPK observed, such as drug 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 and more) at baseline, treatment should not be started.

Drug interactions related to the risk of Myopathy/Rhabdomyolysis

Interacting agents	**Prescribing recommendation**
Cyclosporine, HIV protease inhibitors (tipranavir with ritonavir), hepatitis C protease inhibitor (telaprevir)	Atorvastatin use should be avoided
HIV protease inhibitor (lopinavir and ritonavir)	Use with caution and in the lowest dose necessary
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir with ritonavir*, darunavir with ritonavir, fosamprenavir, fosamprenavir with ritonavir)	Do not exceed 20 mg of atorvastatin daily
HIV protease inhibitors (nelfinavir) Hepatitis C protease inhibitor (boceprevir)	Do not exceed 40 mg of atorvastatin daily
*Use with caution and at the lowest dose necessary.	

Cases of myopathy, including rhabdomyolysis, have been reported with the concomitant administration of atorvastatin and colchicine; caution should be exercised when prescribing colchicine and atorvastatin.

Atorvastatin therapy should be temporarily or permanently discontinued in patients with acute, serious conditions suggestive of myopathy or in patients with predisposing factors that may increase the risk of developing renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disturbances, and uncontrolled seizures).

Diabetes Mellitus and other endocrine effects:

As with other HMG-CoA reductase inhibitors, increases in HbA1c and serum glucose levels have been observed in patients treated with COLASTIN-L. An increased incidence of diabetes has been reported with COLASTIN-L in patients with risk factors for diabetes. However, considering the benefit of HMG-CoA reductase inhibitors by reducing the incidence of major cardiovascular events, the overall balance of benefits and risks appears to be clearly favorable and should therefore not be a reason for discontinuing statin therapy. Patients at risk (fasting blood glucose 5.6 to 6.9 mmol/L, BMI > 30 kg/m^2, increased triglycerides, hypertension) should be monitored clinically and biochemically.

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and may theoretically affect adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol levels or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Cautions should be

observed if an HMG-CoA reductase inhibitor is used concomitantly with drugs that may reduce the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Hemorrhagic stroke:
A post-hoc analysis of a clinical trial in 4731 patients without coronary heart disease (CHD) who had a stroke or transient ischemic attack (TIA) within the past 6 months and who received atorvastatin 80 mg found a higher incidence of hemorrhagic stroke in the atorvastatin 80 mg group compared with the placebo group (55 atorvastatin vs. 33 placebo). Patients with a hemorrhagic stroke at baseline appeared to be at greater risk for recurrent hemorrhagic stroke (7 atorvastatin vs. 2 placebo). However, patients treated with atorvastatin 80 mg had a lower rate of any type of stroke (265 atorvastatin vs. 311 placebo) and a lower rate of CHD-related events (123 vs. 311). (See Section 5.1, Recurrent Stroke.)

Warnings for the patient:
Patients should be advised to promptly report any unexplained muscle pain, tenderness, or weakness, especially if accompanied by malaise or fever.

Pediatric use:
Safety and efficacy in patients aged 10 to 17 years with heterozygous familial hypercholesteremia were evaluated in a 6-month controlled clinical trial. Patients treated with atorvastatin generally had an adverse experience profile similar to that of placebo patients; the most common adverse experiences, regardless of causality assessment, were infections. Doses above 20 mg have not been studied in this patient population. In this limited controlled study, there were no recordable effects on growth or sexual development in boys or on menstrual cycle length in girls. Adequate contraceptive method advice should be advised when atorvastatin is administered to adolescent girls (see sections 4.3, 4.4, and 4.6). Atorvastatin has not been studied in controlled clinical trials involving prepubertal patients or patients younger than 10 years of age. Information on the safety of effects on growth and development in the pediatric population is insufficient.

Geriatric use:
Plasma concentrations of atorvastatin were higher in healthy elderly patients (age 65 years and older) than in young adults (approximately 40% for C_{max} and approximately 30% for AUC). LDL-C reductions were similar to those seen in younger patient populations given equivalent 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 lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; no sodium-related side effects are expected at this dose.

4.5 Interaction with other medicinal products and other forms of interaction

During treatment with HMG-CoA reductase inhibitors, the risk of myopathy increases with concomitant administration of cyclosporine, fibric acid derivatives (e.g., gemfibrozil, fenofibrate), niacin, or cytochrome P450 3A4 inhibitors (e.g., erythromycin, clarithromycin (see below), and azole antifungals) (see Section 4.4, Skeletal Muscle Effects).

The starting daily dose of atorvastatin should be 10 mg in patients taking medications that increase atorvastatin plasma concentrations. A lower maximum atorvastatin dose should be used if clarithromycin and itraconazole are being administered.

Cytochrome P450 3A4 inhibitors:
Atorvastatin is metabolized by cytochrome P450 3A4. Coadministration of atorvastatin with cytochrome P450 3A4 inhibitors may result in increased plasma concentrations of atorvastatin. The degree of interaction and the potentiation of effect depend on the variability of the effect on cytochrome P450 3A4.

Erythromycin/clarithromycin:
Coadministration of erythromycin (500 mg 4 times daily) or clarithromycin (500 mg twice daily), known inhibitors of cytochrome P450 3A4, with atorvastatin has been associated with elevated plasma atorvastatin concentrations (see Section 4.4, Skeletal Muscle Effects). If co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily.

Protease Inhibitors:
Coadministration of atorvastatin with several combinations of HIV protease inhibitors and the hepatitis C protease inhibitor telaprevir significantly increased atorvastatin AUC compared to atorvastatin alone. Therefore, concomitant use of COLASTIN-L should be avoided in patients receiving the HIV protease inhibitor tipranavir and ritonavir or the hepatitis C protease inhibitor telaprevir. Caution should be exercised when prescribing COLASTIN-L in patients receiving the HIV protease inhibitor lopinavir and ritonavir, and the lowest necessary dose should be used. In patients receiving 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 sections 4.2 and 4.4 skeletal muscle effects). In patients receiving 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 use of atorvastatin (40 mg) and diltiazem (240 mg) resulted in increased atorvastatin plasma concentrations.

Cimetidine:
An interaction study with cimetidine has been conducted, and no clinically significant interaction was observed.

Itraconazole:
Concomitant use of atorvastatin (20-40 mg) and itraconazole (200 mg) has been associated with an increase in atorvastatin AUC. If itraconazole and atorvastatin need to be co-administered, the maintenance dose of atorvastatin should not exceed 40 mg daily.

Grapefruit Juice:
Some substances found in grapefruit juice inhibit CYP3A4 and cause increased plasma

concentrations of atorvastatin, especially if consumed in large amounts (>1.2 liters/day).

Cytochrome P450 3A4 inducers:
Coadministration of atorvastatin with cytochrome P450 3A4 inducers (e.g., efavirenz, rifampin) may result in decreased atorvastatin plasma concentrations to varying degrees. Due to the dual mechanism of action of rifampin (cytochrome P450 3A4 induction and inhibition of the hepatocyte uptake transporter OATP1B1), coadministration of atorvastatin with rifampin is recommended. Delayed administration of atorvastatin after rifampin administration results in significant decreases in atorvastatin plasma concentrations.

Antacids:
Coadministration of an oral antacid suspension containing magnesium and aluminum hydroxide with atorvastatin decreased atorvastatin plasma concentrations by approximately 35%, while the rate of LDL-C reduction remained unchanged.

Antipyrine:
Atorvastatin does not affect the pharmacokinetics of antipyrine. Therefore, no interaction is expected with drugs metabolized by the same cytochrome isoenzymes.

Azithromycin:
Coadministration of atorvastatin 10 mg once daily with azithromycin 500 mg once daily did not alter atorvastatin plasma concentrations.

Oral contraceptives:
Coadministration with an oral contraceptive containing norethindrone and ethinyl estradiol increased the AUCs of norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively. These increased concentrations should be considered when selecting oral contraceptive doses for women taking atorvastatin.

Warfarin:
When atorvastatin was administered to patients on chronic warfarin therapy, no clinically significant effects on prothrombin time were observed. However, patients on warfarin should be closely monitored if they require COLASTIN-L.

Amlodipine:
In a drug interaction study conducted in healthy individuals, the 18% increase in atorvastatin concentration following concomitant administration of 80 mg atorvastatin and 10 mg amlodipine was not considered clinically significant.

Colchicine:
Case reports of myopathy, including rhabdomyolysis, have been reported when atorvastatin was used with colchicine; therefore, caution should be exercised when atorvastatin is used concomitantly with colchicine.

Transporter 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 10 mg atorvastatin and 5.2 mg/kg/day cyclosporine resulted in a 7.7-fold increase in atorvastatin exposure.
Concomitant use of atorvastatin and cyclosporine should be avoided. (See Section 4.4, Skeletal

Muscle Effects)

Gemfibrozil:
Due to the increased risk of myopathy/rhabdomyolysis associated with the concomitant use of HMG-CoA reductase inhibitors and gemfibrozil, coadministration of COLASTIN-L with gemfibrozil should be avoided.

Ezetimibe:
The use of ezetimibe alone has been associated with muscle-related events, including rhabdomyolysis. Therefore, the risk of these events may be increased when atorvastatin is used with ezetimibe. Appropriate clinical monitoring of these patients is recommended.

Colestipol:
When colestipol was administered with atorvastatin, plasma concentrations of atorvastatin were lower (approximately 25%). However, the LDL-C reduction observed with atorvastatin and colestipol was greater than that seen when either drug was given alone.

Fusidic acid:
Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems, such as rhabdomyolysis, have been reported with this combination in post-marketing experience. Patients should be closely monitored, and temporary interruption of atorvastatin therapy may be considered.

Digoxin:
Coadministration of multiple doses of atorvastatin 10 mg and digoxin did not affect steady-state plasma digoxin concentrations. However, following daily administration of atorvastatin 80 mg, digoxin concentrations increased by approximately 20%. Patients taking digoxin should be carefully monitored.

Other fibrates:
Because the risk of myopathy is known to increase when other fibrates are used concomitantly with HMG-CoA reductase inhibitors, caution should be exercised when using COLASTIN-L with other fibrates.

Niacin:
The risk of skeletal muscle effects may be increased when COLASTIN-L is used in combination with niacin; in this case, a dose reduction of COLASTIN-L should be considered.

Other concomitant medications:
Clinical studies of atorvastatin used concomitantly with antihypertensive agents and estrogen replacement therapy have not reported evidence of clinically significant adverse interactions. Interaction studies for all specific agents are not available.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: X

Women of child-bearing potential/Birth control (Contraception)
Women of child-bearing potential should use appropriate contraceptive measures during treatment (see section 4.3). Atorvastatin should be used in women of childbearing age only if pregnancy is

considered highly unlikely and if they have been informed of the potential hazard to the fetus.

Pregnancy
Atorvastatin is contraindicated during pregnancy.

Breastfeeding
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).

Reproductive 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 have mostly been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8,755 atorvastatin vs. 7,311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4% 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 COLASTIN-L.

Estimated frequencies of reactions are ranked according to the following convention:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), unknown (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, bullous rashes (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, tendonopathy sometimes complicated by rupture

Reproductive system and breast disorders
Uncommon : impotence
Very rare : gynecomasty

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 contains safety data for 249 pediatric patients receiving atorvastatin. Of these patients, 7 were younger than 6 years, 14 were between 6 and 9 years of age, and 228 were between 10 and 17 years of age.

Nervous system disorders:
Common: Headache

Gastrointestinal disorders:
Common: Abdominal pain

Investigations:
Common: Increased alanine aminotransferase, increased blood creatine phosphokinase

Based on available data, the frequency, type, and severity of adverse events observed in children are expected to be similar to those seen in adults. There is currently limited long-term safety experience in the pediatric population.

The following adverse events have been reported with some statins:
- Sleep disturbance, including insomnia and nightmares.
- Memory loss.
- Sexual dysfunction.
- Depression
- Rare interstitial lung disease, particularly with long-term therapy (see Section 4.4).
- Diabetes: Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥5.6 mmol/L, BMI >30 kg/m^2, increased triglycerides, history of hypertension).

In post-marketing experience, rare cases of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) have been reported in association with statin use. These cognitive problems have been reported for all statins. The reports are generally mild, generally reversible upon discontinuation of the statin, and the time to onset (1 day to years) and resolution (median 3 weeks) of symptoms vary.

Immune-mediated necrotizing myopathy associated with statin use has been reported rarely. 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
There is no specific treatment for overdose of COLASTIN-L. If overdose occurs, the patient should be treated symptomatically and appropriate supportive measures should be implemented. Liver function tests and CPK levels should be monitored. Hemodialysis is not expected to significantly

increase atorvastatin clearance due to extensive drug binding to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiovascular Drugs, Serum Lipid Lowering 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 apoB in patients with homozygous and heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also lowers VLDL-C and triglycerides and produces variable increases in HDL-C.

Triglycerides and cholesterol are incorporated into VLDL (very low-density lipoprotein) in the liver and released into the plasma for transport to peripheral tissues. LDL (low-density lipoprotein) is formed from VLDL and is primarily catabolized via the high-affinity LDL receptor. Cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL, and their remnants, may, like LDL, promote atherosclerosis. Elevated plasma triglycerides are often found in a triple environment with low HDL cholesterol and small LDL particles, which are accompanied by non-lipid metabolic risk factors for coronary heart disease. Total plasma triglycerides alone have not been shown to be a risk factor for coronary heart disease.

Atorvastatin lowers plasma cholesterol and LDL levels by inhibiting HMG-CoA reductase, reduces cholesterol synthesis in the liver, and increases LDL uptake and catabolism by increasing the number of hepatic LDL receptors on the cell surface.

Atorvastatin reduces LDL production and the number of LDL particles, resulting in a large and sustained increase in LDL receptor activity, along with a beneficial change in the quality of circulating LDL particles. Atorvastatin lowers total cholesterol, LDL cholesterol, VLDL cholesterol, apo B, and triglycerides, and increases HDL cholesterol. Atorvastatin lowers IDL cholesterol (intermediate-density lipoprotein) in patients with dysbetalipoproteinemia.

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

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

Atorvastatin and some of its metabolites are pharmacologically active in humans. Atorvastatin's most important site of action is the liver, the primary site of cholesterol synthesis and LDL clearance. LDL-C reduction is related to drug dose rather than systemic drug concentration. Drug

dosage should be individualized 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 evaluated in 10,305 hypertensive patients aged 40 to 80 years (mean 63 years) with no prior history of myocardial infarction or angina treatment and with total cholesterol < 251 mg/dL. All patients also had at least three of the following cardiovascular risk factors: male, age > 55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL ratio > 6, peripheral vascular disease, left ventricular hypertrophy, previous cerebrovascular accident, specific ECG abnormality, and proteinuria/albuminuria. In this double-blind, placebo-controlled study, patients were treated with antihypertensive therapy (target blood pressure <140/90 mm Hg in non-diabetic patients and <130/80 mm Hg in diabetic patients) and randomized to receive atorvastatin 10 mg daily (n=5168) or placebo (n=5137). Good blood pressure control was achieved in both treatment arms. At the interim analysis of this study, the reduction in the risk of cardiovascular events in the atorvastatin-treated group compared to the placebo group exceeded the statistical significance threshold, so the study was terminated earlier than planned (3.3 years) than planned (5 years).

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

Event	Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	P-value
Coronary events (fatal CHD + 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 in fatal and non-fatal strokes did not reach the pre-specified significance level (p=0.01), it showed a positive trend with a 26% relative risk reduction.
The risk reduction was consistent regardless of age, smoking, obesity, and renal dysfunction.
There were no significant differences between the groups in total mortality (p=0.17) and cardiovascular mortality (p=0.51).

The Collaborative Atorvastatin Diabetes Study (CARDS) evaluated the effect of atorvastatin on fatal and nonfatal cardiovascular disease in 2838 type 2 diabetic patients aged 40-75 years, with no history of cardiovascular disease, LDL ≤160 mg/dL, and triglycerides ≤600 mg/dL. All patients also had at least one of the following risk factors: hypertension, smoking, retinopathy, microalbuminuria, or macroalbuminuria. In this randomized, double-blind, multicenter, placebo-controlled study, patients were treated with either 10 mg daily of atorvastatin (n=1428) or placebo (n=1410) for a mean follow-up of 3.9 years. CARDS was terminated 2 years earlier than anticipated because the effect of atorvastatin treatment on the primary endpoint met the pre-specified efficacy discontinuation rule.

The absolute and relative risk reduction effects of Atorvastatin in the CARDS Study were as follows:

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin	p-value

		vs Placebo)	
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 was observed regarding the mortality rate (27% reduction (82 deaths in the placebo group vs. 61 deaths in the treatment arm (p=0.0592)).
The frequency of total adverse events and serious adverse events was similar in both groups.

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 randomized, double- blind, multicentre, 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 mean change from baseline in total atheroma volume (the primary study criterion) was -0.4% (p=0.98) in the atorvastatin group (n=253) and +2.7% (p=0.001) in the pravastatin group (n=249). The effect of atorvastatin was statistically significant compared with pravastatin (p=0.02).

In the atorvastatin group, LDL-C decreased from a baseline of 150 mg/dL ± 28 to a mean of 78.9 mg/dL ± 30, and in the pravastatin group, LDL-C decreased from a baseline of 150 mg/dL ± 26 to a mean of 110 mg/dL ± 26 (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG 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 mean reduction in CRP of 36.4% 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 similar.

Preventing 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, 21-92 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% (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. Atorvastatin 80 mg treatment significantly reduced the risk of major coronary events (HR 0.67; 95% CI, 0.51-0.89; p=0.06), 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 the 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 groups (17 atorvastatin vs. 18 placebo). A reduction in the risk of cardiovascular events with atorvastatin 80 mg was seen in all patient groups except those who entered the study with hemorrhagic stroke and those who had recurrent hemorrhagic shock (7 atorvastatin vs. 2 placebo).

Patients treated with atorvastatin 80 mg had fewer strokes of any type (265 atorvastatin vs. 311 placebo) and CHD events (123 atorvastatin vs. 204 placebo). Total mortality rates were similar between the two groups (216 atorvastatin vs. 211 placebo). There was no difference in the overall incidence of adverse events between treatment groups.

Secondary Prevention of Cardiovascular Events

The Treating to New Targets (TNT) study evaluated the effects of atorvastatin 10 mg/day compared to atorvastatin 80 mg/day in 10,001 individuals (94% white, 81% male, 38% aged ≥65) with clinically established coronary artery disease. These patients achieved an LDL-C target of <130 mg/dL with atorvastatin 10 mg/day at the end of an 8-week, open-label active trial. Patients were then randomized to receive either atorvastatin 10 mg/day or 80 mg/day and followed for a mean of 4.9 years. At week 12, mean LDL-C, TC, TG, non-HDL-C, and HDL-C levels were 73, 145, 128, 98, and 47 mg/dL during treatment with atorvastatin 80 mg and 99, 177, 152, 129, and 48 mg/dL with atorvastatin 10 mg.

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

Risk reduction achieved with atorvastatin 80 mg/day treatment in the TNT study:

Important Result	Atorvastatin 10 mg (N=5006)		Atorvastatin 80 mg (N=4995)		HR[a] (%95 CI)
PRIMARY RESULT*	n	(%)	n	(%)	
First major cardiovascular event	548	(10.9)	434	(8.7)	0.78 (0.69, 0.89)
Components of the primary outcome					
Non-fatal, non-invasive 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 RESULTS**					
First hospitalization with CHF	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 result[b]	615	(12.3)	545	(10.9)	0.88 (0.79, 0.99)

[a] Atorvastatin 80 mg: atorvastatin 10 mg

[b] Components of other secondary outcomes

* Major cardiovascular outcome (MCVE) = death from CHD, nonfatal myocardial infarction, resuscitated cardiac arrest, fatal and nonfatal stroke

** Secondary outcomes not included in the primary outcome

HR = hazard ratio; CI = confidence interval; MI = myocardial infarction; CHF = congestive heart failure; CABG = coronary artery bypass graft
Confidence intervals for secondary outcomes were not adjusted for multiple comparisons.

There was no significant difference in all-cause mortality between treatment groups: 282 (5.6%) in the atorvastatin 10 mg/day group and 284 (5.7%) in the 80 mg/day group. The proportion of patients who experienced cardiovascular death, including CHD death and fatal stroke, was lower in the atorvastatin 80 mg group than in the atorvastatin 10 mg group. The proportion of patients who experienced non-cardiovascular death was higher in the atorvastatin 80 mg group than in the atorvastatin 10 mg group.

The effects of atorvastatin on ischemic events and total mortality were investigated in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. This multicenter, randomized, double-blind, placebo-controlled study enrolled 3,086 patients with acute coronary syndrome (unstable angina and non-Q-wave myocardial infarction). Patients were randomized to receive atorvastatin 80 mg daily or placebo for a median of 16 weeks. In the atorvastatin group, final LDL-C was 72 mg/dL, total-C was 147 mg/dL, HDL-C was 48 mg/dL, and TG was 139 mg/dL. In the placebo group, final LDL-C was 135 mg/dL, total-C was 217 mg/dL, HDL-C was 46 mg/dL, and TG was 187 mg/dL. Atorvastatin significantly reduced the risk of ischemic events and death by 16%. The risk of rehospitalization for documented myocardial ischemia and angina pectoris was significantly reduced by 26%. Atorvastatin reduced the risk of ischemic events and death to similar extents across the entire baseline LDL-C range. In addition, atorvastatin reduced the risk of ischemic events and death to similar extents in patients aged 65 years or older, male or female, with non-Q-wave myocardial infarction and unstable angina.

IDEAL (Additional Decrease in Endpoints Through Aggressive Lipid Lowering Study) compared atorvastatin treatment with simvastatin 20-40 mg/day in 8,888 patients (≤80 years) with a history of coronary heart disease to assess whether either treatment provided additional cardiovascular risk reduction. Most patients were male (81%), white (99%), and had a mean age of 61.7 years. At randomization, the mean LDL-C value was 121.5 mg/dL, and 76% of patients were receiving statin therapy. This prospective, randomized, open-arm, blinded study followed patients for a mean of 4.8 years. With atorvastatin 80 mg treatment, mean LDL-C, total cholesterol, triglyceride, and non-HDL-C values were 78, 145, 115, 45, and 100 mg/dL at 12 weeks, while with simvastatin 20-40 mg/day treatment, they were 105, 179, 142, 47, and 132 mg/dL.

There was no significant difference in the rate of first major cardiovascular event (fatal CHD, nonfatal myocardial infarction, cardiovascular arrest with resuscitation) between the two treatment arms, which was the primary endpoint of the study (411 (9.3%) events in the atorvastatin 80 mg/day arm vs. 463 (10.4%) events in the simvastatin 20-40 mg/day arm, HR 0.89 95% CI (0.78-1.01), p=0.007). There was no difference in all-cause mortality rates between the two treatment arms (366 (8.2%) in the atorvastatin 80 mg arm vs. 374 (8.4%) in the simvastatin 20-40 mg arm). The rates of cardiovascular and non-cardiovascular deaths were similar in 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 postmenarcheal girls aged 10 to 17 years (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 criteria were 1) a baseline LDL-C level of ≥190 mg/dL or 2) a baseline LDL-C level of ≥160 mg/dL and a 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 with 230.0 mg/dL (range: 160.0-324.5 mg/dL) in the placebo group. Atorvastatin dosage (once daily) was 10 mg for the first 4 weeks and was titrated to 20 mg in patients with LDL-C levels >130 mg/dL. The number of patients requiring an increase to 20 mg after week 4 in the double-blind phase was 80 (57.1%) in the atorvastatin-treated group.
Atorvastatin significantly reduced plasma total-C, triglyceride, and apolipoprotein B levels during the 26-week double-blind phase.

Lipid-Lowering Effect of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percent Difference from Baseline at Endpoint in the 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 LDL-C level during the 26-week double-blind phase was 130.7 mg/dL (range: 70.0-242.0 mg/dL) in the atorvastatin group, compared with 228.5 mg/dL (range: 152.0-385.0 mg/dL) in the placebo group.

In this limited, controlled study, there was no detectable effect on menstrual cycle duration in girls or sexual maturation and growth in boys. Atorvastatin has not been studied in controlled clinical trials in prepubertal patients or children under 10 years of age. The safety and efficacy of doses above 20 mg have not been established in controlled trials in children. The long-term effectiveness of atorvastatin therapy taken in childhood in reducing morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Absorption:
Atorvastatin is rapidly absorbed after oral administration, with maximum plasma concentrations occurring within 1 to 2 hours. The extent of absorption and plasma atorvastatin concentrations increase in proportion to the 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 presystemic clearance in the gastrointestinal mucosa and/or first-pass hepatic metabolism. Although food reduces the rate and extent of drug absorption by approximately 25% and 9%, as assessed by C_{max} and AUC, LDL-C reductions are similar whether atorvastatin is administered with or without food. Plasma atorvastatin concentrations are lower after evening administration than after morning administration (approximately 30% for C_{max} and AUC). However, LDL-C reduction is the same regardless of the time of drug administration (see Section 4.2).

Distribution:
The mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins. The red blood cell/plasma ratio is approximately 0.25, indicating poor red blood cell penetration.

Biotransformation:
Atorvastatin is extensively metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro*, its inhibition of HMG-CoA reductase via ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of the circulating inhibitory activity of HMG-CoA reductase is due to active metabolites. Consistent with the increased plasma concentrations of atorvastatin in humans when co-administered with erythromycin, a known inhibitor of cytochrome P450 3A4, in vitro studies indicate the importance of atorvastatin's metabolism by hepatic cytochrome P450 3A4. Additionally, *in vitro* studies indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin with terfenadine, a compound extensively metabolized by cytochrome P450 3A4, does not affect terfenadine plasma concentrations to a clinically relevant extent. Therefore, atorvastatin is not expected to significantly alter the pharmacokinetics of other cytochrome P450 3A4 substrates (see Section 4.5). In animals, the ortho-hydroxy metabolites undergo 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. The 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 20-30 hours due to the contribution of active metabolites. Less than 2% of an orally administered dose of atorvastatin is detected in urine.

Characteristic features of patients
Elderly:
Plasma concentrations of atorvastatin are higher in healthy elderly patients (≥65 years) than in young adults (approximately 40% for C_{max} and 30% for AUC). The ACCESS study specifically evaluated elderly patients with regard to achieving NCEP treatment goals. 1087 patients aged <65 years, 815 patients aged ≥65 years, and 185 patients aged ≥75 years participated in the study. No differences in safety, efficacy, or achievement of lipid therapy goals were observed between elderly patients and the overall population.

Pediatric population:
No pharmacokinetic data are available in the pediatric population.

Gender:
Atorvastatin plasma concentrations differ in women compared to men (C_{max} is approximately 20% higher and AUC is approximately 10% lower in women), but there were no clinically relevant differences in lipid-lowering effects between men and women.

Renal impairment:
Renal disease does not affect atorvastatin plasma concentrations or LDL-C lowering; therefore, dose adjustment is not necessary in patients with renal impairment (see section 4.2).

Hemodialysis:
Studies have not been conducted in patients with end-stage renal disease. Hemodialysis is not expected to significantly increase atorvastatin clearance because the drug is highly bound to plasma proteins.

Hepatic impairment:

Atorvastatin plasma concentrations are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B) (See section 4.3).

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.

Drug Interactions

The effects of co-administered drugs on the pharmacokinetics of atorvastatin and of atorvastatin on the pharmacokinetics of co-administered drugs are presented in the table below (see sections 4.4 and 4.5).

Effect of Co-Administered Medications on the Pharmacokinetics of Atorvastatin

Co-administered medicinal product and dosing regimen	**Atorvastatin**		
	Doz (mg)	**Change in Area Under the Curve (AUC)[&]**	**Change in Cmax[&]**
[#]Cyclosporine 5.2 mg/kg/day, stable dose	10 mg once daily for 28 days	↑8.7 times	↑10.7 times
[#] Tipranavir 500 mg twice daily / ritonavir 200 mg twice daily for 7 days	Single dose 10 mg	↑9.4 times	↑8.6 times
[#]Telaprevir 750 mg q8h, 10 days	Single dose 20 mg	↑7.88 times	↑10.6 times
[#‡] Saquinavir 400 mg twice daily / ritonavir 400 mg twice daily for 15 days	40 mg once daily for 4 days	↑3.9 times	↑4.3 times
[#]Clarithromycin 500 mg twice daily for 9 days	80 mg once daily for 8 days	↑4.4 times	↑5.4 times
[#] Darunavir 300 mg twice daily / ritonavir 100 mg twice daily for 9 days	10 mg once daily for 4 days	↑3.4 times	↑2.25 times
[#] Itraconazole 200 mg, once daily, 4 days	Single dose 40 mg	↑3.3 times	↑%20
[#] Fosamprenavir 700 mg twice daily / ritonavir 100 mg twice daily, 14 days	10 mg once daily for 4 days	↑2.53 times	↑2.84 times
[#] Fosamprenavir 1400 mg twice daily for 14 days	10 mg once daily for 4 days	↑2.3 times	↑4.04 times
[#] Nelfinavir 1250 mg twice daily for 14 days	10 mg once daily for 28 days	↑%74	↑2.2 times

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

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

See Sections 4.4 and 4.5 for clinical significance

* Significant increases in 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 or more per day).

**Single sample taken 8-16 hours after dosing.

† Due to the dual interaction mechanism of rifampin, concomitant administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after rifampin has been associated with a significant decrease in atorvastatin plasma concentrations.

‡ The saquinavir and ritonavir dose in this study is not clinically used. The increase in atorvastatin exposure is expected to be greater than in this study when used clinically. Therefore, caution should be exercised, and the lowest necessary dose should be used.

Effect Of Atorvastatin On The Pharmacokinetics Of Co-Administered Medications

Atorvastatin	**Concomitant medication and dosage regimen**		
	Drug/Dose (mg)	**Change in Area Under the Curve (AUC)&**	**Change in Cmax&**

80 mg once daily for 15 days	Antipyrine, Single dose 600 mg	↑%3 times	↓%11 times
80 mg once daily for 14 days	[#] Digoxin, 0.25 mg once daily, 20 days	↑%15 times	↑%20 times
40 mg once daily for 22 days	Once-daily oral contraceptive, 2 months – 1 mg nortindrone – 35 µg ethinyl estradiol	 ↑%28 times ↑%19 times	 ↑%23 times ↑%30 times
Single dose 10 mg	Tipranavir 500 mg twice daily/ritonavir 200 mg twice daily for 7 days	No change	No change
10 mg once daily for 4 days	Fosamprenavir 1400 mg twice daily, 14 days	↓%27	↓%18
10 mg once daily for 4 days	Fosamprenavir 700 mg twice daily/ritonavir 100 mg twice daily, 14 days	No change	No change

[&]% change = % change ratio [(I-B)/B], I = pharmacokinetic value during the interaction phase, B = pharmacokinetic value during the 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 8-16 times higher based on AUC(0-24). In a 2-year study in mice, the incidence of hepatocellular adenoma in males and hepatocellular carcinoma in females was increased 250-fold at the maximum dose used compared to the highest human dose on a mg/kg body weight basis. Systemic availability was 6-11 times higher based on AUC(0-24). All chemically similar drugs in this class induced tumors in both mice and rats at 12 to 125 times the highest recommended clinical dose on a mg/kg body weight basis.

Atorvastatin did not show mutagenic or clastogenic potential in *in vitro* tests with and without metabolic activation (AMES test with *Salmonella typhimurium* and *Escherichia coli*, *in vitro* HGPRT forward mutation assay in Chinese hamster lung cells, and chromosomal abeation assay in Chinese hamster lung cells). Atorvastatin was also negative in the *in vivo* mouse micronucleus assay.

In animal studies, no adverse effects on fertility or reproduction were observed in male and female rats at doses of up to 175 to 225 mg/kg/day of atorvastatin. These doses are 100 to 140 times the maximum recommended human dose on a mg/kg body weight basis. Atorvastatin given at doses of 10, 40, or 120 mg/kg for two years produced no adverse effects on sperm or semen parameters or reproductive organ histopathology in dogs.

There is evidence from experimental animal studies that HMG-CoA reductase inhibitors may affect embryonic and fetal development. Atorvastatin had no effect on fertility in rats, rabbits, and dogs and was not teratogenic. However, fetal toxicity was observed in rats and rabbits at maternally toxic doses. During dam exposure to high doses of atorvastatin, development of rat offspring was delayed and postnatal survival was reduced. There is evidence of placental transfer in rats. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is unknown 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

48 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 formed aluminum foil (Formpack) on the other.
Each carton box contains 30 or 90 tablets.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

209/85

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