



## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

COLASTIN-L 10 mg Film Coated Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance:**

Atorvastatin calcium ..... 10.825 mg  
equivalent to 10 mg Atorvastatin

**Excipient(s):**

Lactose monohydrate (from cow milk) ..... 41.5 mg  
For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Film coated tablet.

White, oblong, film-coated, homogenous tablets embossed “10” on one side.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

**Hypercholesterolemia**

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (TC), LDL-cholesterol, apolipoprotein B (Apo 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.

Atorvastatin 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:**

Atorvastatin is 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 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 section 4.4 and 5.2).

**Hepatic impairment:**

COLASTIN-L should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). COLASTIN-L is contraindicated in patients with active liver disease (see section 4.3).

**Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10–17 years of age)**

The recommended starting dose of COLASTIN-L is 10 mg daily (see section 5.1). Depending on response and tolerability, the daily dose may be increased up to 80 mg.

The dose should be individualized according to the recommended treatment goal. Dose adjustments should be made at least every 4 weeks.

Titration of the daily dose to 80 mg is supported by data from studies in adults and limited clinical data from studies in pediatric patients with heterozygous familial hypercholesterolemia (see sections 4.8 and 5.1). Limited safety and efficacy data are available from open-label studies in pediatric patients with heterozygous familial hypercholesterolemia aged 6 to 10 years. Atorvastatin is not indicated for the treatment of patients younger than 10 years. Available data are described in Sections 4.8, 5.1, and 5.2, but no posology recommendation can be made.

Other pharmaceutical forms and strengths may be more appropriate for this patient group.

**Geriatric population:**

No difference in efficacy and safety was observed between elderly patients and general population (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 Hydroxymethylglutaryl-Coenzyme A (HMG-KoA) 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).

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

Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin (see sections 4.4 and 4.5).

**4.3 Contraindications**

COLASTIN-L is contraindicated in following patients:

- With hypersensitivity to atorvastatin or any other component of this medicinal product listed in 6.1
- With active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (ULN)
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures
- Treated with the hepatitis C antivirals glecaprevir/pibrentasvir

Atorvastatin is not indicated for the treatment of patients under 10 years of age.

**4.4 Special warnings and precautions for use**

**Liver effects:**

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

COLASTIN-L should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

### **Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)**

In a post-hoc analysis of stroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

### **Skeletal muscle effects**

Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterized by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinemia and myoglobinuria which may lead to renal failure.

There have been very rare reports of an immune mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

### **Before treatment in patients at risk of rhabdomyolysis:**

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK 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 consumption
- 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 CK 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 CK levels are significantly elevated (5 times and more) at baseline, treatment should not be started.

### *Creatine kinase measurement*

Creatine kinase should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (>5 times ULN), levels should be remeasured within 5 to 7 days later to confirm the results.



### **Whilst on treatment**

- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.
- If such symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels should be measured. If these levels are found to be significantly elevated (>5 times ULN), treatment should be stopped.
- If muscle symptoms are severe and cause daily discomfort, discontinuation of treatment should be considered even if the increase in CK levels is less than 5 times the ULN.
- If symptoms resolve and CK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Atorvastatin must be discontinued if clinically significant elevation of CK levels (>10×ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

### Concomitant treatment with other medicines

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, letermovir and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivatives, antivirals for the treatment of hepatitis C (HCV) (boceprevir, telaprevir, elbasvir/grazoprevir), erythromycin, niacin or ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. If patients are taking medications that may increase plasma concentrations of atorvastatin, it is recommended that the maximum dose of atorvastatin be reduced. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or for 7 days after fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis cases (some of them fatal) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be informed that they should seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g., for the treatment of severe infections, the need for co-administration of COLASTIN-L and fusidic acid should only be considered on a case by case basis and under close medical supervision.

### Pediatric population

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



#### Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include 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.

#### Diabetes Mellitus

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.

Some evidence suggests that statins as a class raise blood glucose levels and lead to hyperglycemia levels that may lead to regular diabetes treatment in some patients at risk of developing diabetes in the future.

However, the reduction in vascular risk with statins outweighs this risk and therefore should not be considered a reason to discontinue statin therapy. Patients at risk (fasting blood glucose 100.9–124.3 mg/dl, body mass index (BMI) >30 kg/m<sup>2</sup>, elevated triglycerides, hypertension) should be monitored either clinically or biochemically according to national guidelines.

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.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### Effect of co-administered medications on atorvastatin

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medications that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 4.3 and 4.4).

#### CYP3A4 inhibitors

Potent CYP3A4 inhibitors have been shown to lead to markedly increased concentrations of atorvastatin (see Table 1 and specific information below). Co-administration of potent CYP3A4 inhibitors (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole, some antivirals used in the treatment of HCV (e.g., elbasvir/grazoprevir), and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc.) should be avoided if possible. In cases where co-administration of these medications with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has

been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

#### CYP3A4 inducers

Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John's Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (CYP3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

#### Transport inhibitors

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

Use of atorvastatin is not recommended in patients taking letermovir co-administered with ciclosporin (see section 4.4 and 4.5).

#### Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

#### Ezetimibe

The use of ezetimibe alone is associated with muscle related events, including rhabdomyolysis. The risk of these events may therefore be increased with concomitant use of ezetimibe and atorvastatin. Appropriate clinical monitoring of these patients is recommended.

#### Colestipol

When colestipol was administered concomitantly with atorvastatin calcium, the plasma concentrations of atorvastatin and its active metabolites were found to be lower (atorvastatin concentration ratio 0.74). However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

#### Fusidic acid

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



If treatment with systemic fusidic acid is necessary, atorvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Colchicine

Although interaction studies with atorvastatin and colchicine have not been conducted, cases of myopathy have been reported with atorvastatin co-administered with colchicine, and caution should be exercised when prescribing atorvastatin with colchicine.

Effect of atorvastatin on co-administered medications

Digoxin

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

Oral contraceptives

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

Warfarin

In a clinical study in patients receiving warfarin therapy, co-administration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of initiating atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. In patients not taking anticoagulants, atorvastatin therapy does not cause bleeding or changes in prothrombin time.

Drug interactions

**Table 1: Effect of co-administered medications on the pharmacokinetics of atorvastatin**

| Co-administered medication and dosing regimen                       | Atorvastatin                    |                               |  |
|---|---------------------------------|-------------------------------|--|
|   | Dose (mg)                       | Ratio of AUC <sup>&amp;</sup> | Clinical Recommendation <sup>#</sup>   |
| Glecaprevir 400 mg OD/<br>Pibrentasvir 120 mg OD, 7 days            | 10 mg OD for 7 days             | 8.3                           | Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).   |
| Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21) | 40 mg on day 1, 10 mg on day 20 | 9.4                           | In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended. |
| Telaprevir 750 mg every 8 hours, 10 days                            | 20 mg, SD                       | 7.9                           |  |
| Ciclosporin 5.2 mg/kg/day, stable dose                              | 10 mg OD for 4 days             | 8.7                           |  |
| Lopinavir 400 mg BID/ Ritonavir                                     | 20 mg OD for 4                  | 5.9                           | In cases where co-administration   |



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|   |                      |        |  |
|---|----------------------|--------|--|
| 100 mg BID, 14 days   | days                 |        | with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.                                  |
| Clarithromycin 500 mg BID, 9 days   | 80 mg OD for 8 days  | 4.5    |  |
| Saquinavir 400 mg BID/ Ritonavir 100 mg (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing | 40 mg OD for 4 days  | 3.9    | In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended. |
| Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days  | 10 mg OD for 4 days  | 3.4    |  |
| Itraconazole 200 mg OD, 4 days  | 40 mg SD             | 3.3    |  |
| Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days   | 10 mg OD for 4 days  | 2.5    |  |
| Fosamprenavir 1400 mg BID, 14 days  | 10 mg OD for 4 days  | 2.3    |  |
| Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days   | 10 mg SD             | 1.95   | The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.  |
| Letemovir 480 mg OD, 10 days  | 20 mg SD             | 3.29   | The dose of atorvastatin should not exceed a daily dose of 20 mg during co administration with products containing letemovir.  |
| Nelfinavir 1250 mg BID, 14 days   | 10 mg OD for 28 days | 1.74   | No specific recommendation.  |
| Grapefruit Juice, 240 ml OD *   | 40 mg, SD            | 1.37   | Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.  |
| Diltiazem 240 mg OD, 28 days  | 40 mg, SD            | 1.51   | After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.   |
| Erythromycin 500 mg QID, 7 days   | 10 mg, SD            | 1.33   | Lower maximum dose and clinical monitoring of these patients is recommended.   |
| Amlodipine 10 mg, single dose   | 80 mg, SD            | 1.18   | No specific recommendation.  |
| Cimetidine 300 mg QID, 2 weeks  | 10 mg OD for 2 weeks | 1.00   | No specific recommendation.  |
| Colestipol 10 g BID, 24 weeks   | 40 mg OD for 8 weeks | 0.74** | No specific recommendation   |
| Antacid suspension of magnesium and aluminum hydroxides, 30 ml QID, 17 days   | 10 mg OD for 15 days | 0.66   | No specific recommendation.  |
| Efavirenz 600 mg OD, 14 days  | 10 mg for 3 days     | 0.59   | No specific recommendation.  |
| Rifampin 600 mg OD, 7 days (co-administered)  | 40 mg SD             | 1.12   | If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.   |
| Rifampin 600 mg OD, 5 days (doses separated)  | 40 mg SD             | 0.20   |  |

|                                |          |      |  |
|--------------------------------|----------|------|--|
| Gemfibrozil 600 mg BID, 7 days | 40 mg SD | 1.35 | Lower starting dose and clinical monitoring of these patients is recommended.  |
| Fenofibrate 160 mg OD, 7 days  | 40 mg SD | 1.03 | Lower starting dose and clinical monitoring of these patients is recommended.  |
| Boceprevir 800 mg TID, 7 days  | 40 mg SD | 2.3  | Lower starting dose and clinical monitoring of these patients is recommended. The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with boceprevir. |

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

# See sections 4.4 and 4.5 for clinical significance.

\* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medications metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased Area Under the Curve (AUC) of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold.

\*\* Ratio based on a single sample taken 8-16 h post dose.

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

**Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medications**

| Atorvastatin and dosing regimen | Co-administered medicinal product  |                               |  |
|---------------------------------|--|-------------------------------|--|
|                                 | Medication/Dose (mg)   | Ratio of AUC <sup>&amp;</sup> | Clinical Recommendation                                    |
| 80 mg OD for 10 days            | Digoxin 0.25 mg OD, 20 days  | 1.15                          | Patients taking digoxin should be monitored appropriately. |
| 40 mg OD for 22 days            | Oral contraceptive OD, 2 months<br>- norethindrone 1 mg<br>- ethinyl estradiol 35 µg | 1.28                          | No specific recommendation.                                |
|                                 |  | 1.19                          |  |
| 80 mg OD for 15 days            | * Phenazone, 600 mg SD   | 1.03                          | No specific recommendation.                                |
| 10 mg, SD                       | Tipranavir 500 mg BID/ritonavir 200 mg BID, 7 days                                   | 1.08                          | No specific recommendation.                                |
| 10 mg, OD for 4 days            | Fosamprenavir 1400 mg BID, 14 days   | 0.73                          | No specific recommendation.                                |
| 10 mg OD for 4 days             | Fosamprenavir 700 mg BID/ritonavir 100 mg BID, 14 days                               | 0.99                          | No specific recommendation.                                |

& Represents ratio of treatments (co-administered drug plus atorvastatin versus atorvastatin alone).

\* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

OD = once daily; SD = single dose; BID = twice daily.

### Drug interactions related to the risk of myopathy/rhabdomyolysis

| Interacting agents  | Prescribing recommendation                         |
|---|--|
| Cyclosporine, HIV protease inhibitors (tipranavir and 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 effective dose  |   |

### **Additional Information on Special Populations**

No data is available for special populations.

### **Pediatric population:**

Drug interaction studies have been conducted only in adults. The extent of interactions in the pediatric population is unknown. For pediatric populations, the interactions mentioned above for adults and the precautions in section 4.4 should be considered.

## **4.6 Fertility, 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).

### **Pregnancy**

Atorvastatin is contraindicated during pregnancy (see section 4.3). The safety of atorvastatin calcium trihydrate in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Animal studies have shown reproductive toxicity (see section 5.3).

Treatment of pregnant women with atorvastatin may reduce fetal levels of mevalonate, a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering medications during pregnancy will have only a minor impact on the long-term outcome of primary hypercholesterolemia.

For these reasons, COLASTIN-L should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with COLASTIN-L should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant (see section 4.3).

### **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**

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



#### 4.7 Effects on ability to drive and use machines

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

#### 4.8 Undesirable effects

In the atorvastatin placebo-controlled clinical trial database of 16,066 (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 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 ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), unknown (cannot be estimated based on 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 disorders, connective tissue and bone diseases:**

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

#### **Reproductive system and breast disorders**

*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 calcium trihydrate. 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 the ULN occurred in 2.5% of patients receiving atorvastatin, similar to those observed with other HMG-CoA reductase inhibitors in clinical trials. Values greater than 10 times the ULN occurred in 0.4% of patients treated with atorvastatin (see section 4.4).

#### ***Pediatric Population***

Pediatric patients aged from 10 to 17 years of age treated with atorvastatin had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups (regardless of causality assessment) were infections. No clinically significant effect on growth and sexual maturation was observed in a 3-year study based on the assessment of overall maturation and development, assessment of Tanner Stage, and measurement of height and weight. The safety and tolerability profile in pediatric patients was similar to the known safety profile of atorvastatin in adult patients.

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

***The following adverse events have been reported with some statins:***

- Sleep disturbances including insomnia and having nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Rare 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 100.9 mg/dl, BMI >30 kg/m<sup>2</sup>, raised triglycerides, history of hypertension).

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 atorvastatin calcium trihydrate overdose. If 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 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 to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

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

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



lowering medicinal products.

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

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

#### Homozygous familial hypercholesterolemia

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

#### Atherosclerosis

The Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study evaluated the effects of intensive lipid-lowering therapy with atorvastatin and standard lipid-lowering therapy with pravastatin 40 mg on coronary atherosclerosis in patients with coronary artery disease by intravenous ultrasound (IVUS) at the time of angiography. In this randomized, double-blind, multicenter, controlled clinical trial, 502 patients underwent IVUS at baseline and 18 months.

In the atorvastatin group (n=253), there was no progression of atherosclerosis.

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

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

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

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

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

#### Acute coronary syndrome

In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina).

Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischemia requiring hospitalization, indicating a risk reduction by 16% ( $p=0.048$ ). This reduction was mainly due to a 26% reduction in re-hospitalization for angina pectoris with evidence of myocardial ischemia ( $p=0.018$ ). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

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

#### Prevention of cardiovascular disease

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

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

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

| Event  | Relative Risk Reduction (%) | No. of Events (Atorvastatin vs Placebo) | Absolute Risk Reduction <sup>1</sup> (%) | p-value |
|--|-----------------------------|---|--|---------|
| Fatal CHD plus non-fatal MI                                  | 36%                         | 100 vs. 154                             | 1.1%                                     | 0.0005  |
| Total cardiovascular events and revascularization procedures | 20%                         | 389 vs. 483                             | 1.9%                                     | 0.0008  |
| Total coronary events  | 29%                         | 178 vs 247                              | 1.4%                                     | 0.0006  |

<sup>1</sup>Based on difference in crude events rates occurring over a median follow-up of 3.3 years.

CHD = coronary heart disease; MI = myocardial infarction.

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

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

retinopathy, microalbuminuria or macroalbuminuria.

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

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

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

<sup>1</sup>Based on difference in crude events rates occurring over a median follow-up of 3.9 years.

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

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

#### Recurrent stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 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 (3.4 mmol/L). The mean LDL-C was 73 mg/dl (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dl (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

Atorvastatin 80 mg reduced the risk of the primary endpoint of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. All cause mortality was 9.1% (216/2365) for atorvastatin versus 8.9% (211/2366) for placebo.

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.

- Among patients who entered the study with a prior hemorrhagic stroke, the risk of hemorrhagic stroke (7/45 for atorvastatin vs. 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and ischemic stroke were similar between groups (3/45 for atorvastatin vs. 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).
- The risk of hemorrhagic stroke was increased in patients who entered the study with prior lacunar infarct (20/708 for atorvastatin versus 4/701 for placebo; HR 4.99; 95% CI, 1.71-14.61), but the risk of ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

All cause mortality was 15.6% (7/45) for atorvastatin versus 10.4% (5/48) in the subgroup of patients with prior hemorrhagic stroke. All cause mortality was 10.9% (77/708) for atorvastatin



versus 9.1% (64/701) for placebo in the subgroup of patients with prior lacunar infarct.

### ***Pediatric population***

#### ***Heterozygous Familial Hypercholesterolemia in Pediatric Patients aged 6-17 years old***

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolemia and baseline LDL-C  $\geq 4$  mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage  $\geq 2$ .

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

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

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

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

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



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

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

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

Heterozygous Familial Hypercholesterolemia in Pediatric Patients aged 10-17 years old

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

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

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

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

The European Medicines Agency has waived the obligation to submit the results of studies with atorvastatin in children aged 0-6> years for the treatment of heterozygous hypercholesterolemia and in children aged 0-18> years for the prevention of homozygous familial hypercholesterolemia, combined (mixed) hypercholesterolemia, primary hypercholesterolemia, and cardiovascular events (For information on pediatric use, see Section 4.2).

## 5.2 Pharmacokinetic properties

### General 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 increases in proportion to atorvastatin dose. Atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and



the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

#### Distribution

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

#### Biotransformation

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

#### Elimination

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

Atorvastatin is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the efflux transporters multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see Section 5.2).

### ***Characteristic features of patients***

#### Elderly

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

#### Pediatric population

In an open-label, 8-week study, pediatric patients aged 6 to 17 years with heterozygous familial hypercholesterolemia, Tanner Stage 1 (n=15) and Tanner Stage 2 or later (n=24), and baseline LDL-C  $\geq 4$  mmol/L were treated with atorvastatin 5 or 10 mg chewable tablets or 10 or 20 mg film-coated tablets, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in pediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

#### Gender

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

#### Renal impairment



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

#### Hepatic impairment

Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in  $C_{max}$  and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B) (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. It may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

### **5.3 Preclinical safety data**

A series of tests (4 *in vitro* and 1 *in vivo*) have shown that atorvastatin has no mutagenic or clastogenic potential. Atorvastatin was not carcinogenic in rats, but in mice, at high doses (ending at 6-11 times the  $AUC_{0-24}$  value achieved at the highest recommended human dose), hepatocellular adenomas were observed in males and hepatocellular carcinomas in females.

There is evidence from animal experimental animal 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. During exposure of mothers to high doses of atorvastatin, the development of rat pups was delayed and postnatal survival was reduced. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose monohydrate (from cow milk)

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 formed aluminum foil (Formpack) on the other.

Each 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**

209/82

## **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**