

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin Mylan 10 mg film-coated tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:

Each tablet contains 42.5 mg of lactose and 0.1 mg of soya lecithin.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet.

White, oval, biconvex, film coated tablet, approximately 9.2mm × 4.7mm, plain on one side and debossed '10' on the other side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

#### Hypercholesterolaemia

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

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

#### Prevention of Cardiovascular Disease

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

### 4.2 Posology and method of administration

#### Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving atorvastatin and should continue on this diet during treatment with Atorvastatin Mylan.

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

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

#### *Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia*

The majority of patients are controlled with Atorvastatin Mylan 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

#### *Heterozygous familial hypercholesterolaemia*

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

#### *Homozygous familial hypercholesterolaemia*

Only limited data are available (see section 5.1)

The dose of atorvastatin in patients with homozygous familial hypercholesterolaemia 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 dosages may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

#### *Co-administration with other medicines*

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

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#### *Patients with renal impairment*

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

#### *Patients with hepatic impairment*

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

#### *Elderly*

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

#### *Paediatric population*

##### *Hypercholesterolaemia*

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

For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day (see section 5.1). The dose may be increased to 80 mg daily, according to the response and tolerability.

Doses should be individualised according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg daily is supported by study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia (see sections 4.8 and 5.1).

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6-10 years of age derived from open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

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

#### Method of administration

Atorvastatin Mylan is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Atorvastatin Mylan contains soya lecithin. Patients who are allergic to peanut or soya, should not use this medicinal product.
- Patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).
- Patients treated with the hepatitis C antivirals glecaprevir/pibrentasvir.

#### 4.4 Special warnings and precautions for use

##### Liver Effects

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

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

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

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

##### Skeletal muscle effects

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

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

##### *Before the treatment*

Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In the elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2) In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended. If CK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

##### *Creatine kinase measurement*

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

#### *Whilst on treatment*

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

#### *Concomitant treatment with other medicinal products*

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, voriconazole, itraconazole, ketoconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, tipranavir/ritonavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid 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. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

Atorvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination (see section 4.5). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness.

Statin therapy may be re-introduced seven days after the last dose of fusidic acid.

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

#### Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

#### Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/L, BMI > 30kg/m<sup>2</sup>, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Paediatric population

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

Excipients

Atorvastatin Mylan contains lactose. Patients with rare hereditary problems of galactose intolerance, total Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Atorvastatin Mylan contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**4.5 Interaction with other medicinal products and other forms of interactions**Effect of co-administered medicinal products on atorvastatin

Atorvastatin is metabolised by cytochrome P450 3A4 (CYP3A4) and is a substrate of the hepatic transporters, organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3) transporter. Metabolites of atorvastatin are substrates of OATP1B1. Atorvastatin is also identified as a substrate of the multi-drug resistance protein 1 (MDR1) and breast cancer resistance protein (BCRP), which may limit the intestinal absorption and biliary clearance of atorvastatin (see section 5.2). Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivatives and ezetimibe (see section 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, voriconazole, itraconazole, ketoconazole, 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 medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended (see Table 1).

*Moderate CYP3A4 inhibitors* (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1). An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

*CYP3A4 inducers*

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

*Transport inhibitors*

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

*Gemfibrozil/ fibric acid derivatives*

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

*Ezetimibe*

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

*Colestipol*

Plasma concentrations of atorvastatin and its active metabolites were lower (ratio of atorvastatin concentration: 0.74) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

*Fusidic acid*

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

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

*Colchicine*

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

Effect of atorvastatin on co-administered medicinal products

*Digoxin*

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

*Oral Contraceptives*

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

*Warfarin*

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

Paediatric population

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

Drug Interactions

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

Co-administered medicinal product and dosing regimen	Atorvastatin				
	Dose (mg)		Ratio of AUC <sup>&amp;</sup>		Clinical recommendation#

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
Ciclosporin 5.2mg/kg/day, stable dose		10 mg OD for 28 days		8.7	
Glecaprevir 400 mg OD/ Pibrentasvir 120 mg OD, 7 days		10 mg OD for 7 days		8.3	Co-administration with products containing glecaprevir or pibrentasvir is contraindicated (see section 4.3).
Telaprevir 750 mg q8h, 10 days		20 mg, SD		7.9	In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days		20 mg OD for 4 days		5.9	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days		80 mg OD for 8 days		4.5	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 4-18, 30 min after atorvastatin dosing		40 mg OD for 4 days		3.9	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days		10 mg OD for 4 days		3.4	
Itraconazole 200 mg OD, 4 days		40 mg, SD		3.3	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days		10 mg OD for 4 days		2.5	
Fosamprenavir 1400 mg BID, 14 days		10 mg OD for 4 days		2.3	
Boceprevir 800 mg TID, 7 days		40mg 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 coadministration with boceprevir.

Elbasvir 50 mg OD/ Grazoprevir 200 mg OD, 13 days		10 mg SD		1.95	The dose of atorvastatin should not exceed a daily dose of 20 mg during co-administration with products containing elbasvir or grazoprevir.
Nelfinavir 1250 mg BID, 14 days		10 mg OD for 28 days		1.74	No specific recommendation
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.
Grapefruit Juice, 240 mL OD *		40 mg, SD		1.37	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Gemfibrozil 600 mg BID, 7 days		40 mg, SD		1.35	Lower starting dose and 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
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.
Fenofibrate 160 mg OD, 7 days		40 mg, SD		1.03	Lower starting dose and clinical monitoring of these patients is recommended.
Cimetidine 300 mg QID, 2 weeks		10 mg OD for 2 weeks		1.00	No specific recommendation
Colestipol 10 g BID 24 weeks		40 mg OD for 8 weeks		0.74**	No specific recommendation
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 17 days		10 mg OD for 15 days		0.66	No specific recommendation
Efavirenz 600 mg OD, 14 days		10 mg for 3 days		0.59	No specific recommendation
Rifampin 600 mg OD, 5 days (doses separated)		40 mg, SD		0.20	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.

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

# See sections 4.4 and 4.5 for clinical significance.

\* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active



orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5-fold and AUC of active (atorvastatin and metabolites). HMG-CoA reductase inhibitors 1.3-fold.

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

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

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

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

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

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

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

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy

Atorvastatin Mylan is contraindicated during pregnancy (see section 4.3). Safety in pregnant women has not been established. No controlled clinical trials with atorvastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. Studies in animals have shown toxicity to reproduction (see section 5.3).

Maternal treatment with atorvastatin may reduce the foetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolaemia.

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

##### Breast-feeding

It is not known whether atorvastatin or its metabolites are excreted in human milk. In rats, plasma concentrations of atorvastatin and its active metabolites are similar to those in milk (see section 5.3). Because of the potential for serious adverse reactions, women taking Atorvastatin Mylan should not breast-feed their infants (see section 4.3). Atorvastatin is contraindicated during breastfeeding (see section 4.3).

##### Fertility

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

##### Women of childbearing potential

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

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

Atorvastatin 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 mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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

Estimated frequencies of reactions are ranked according to the following convention: Common ( $\geq 1/100$  to  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); Very rare ( $< 1/10,000$ ), Not known (cannot be estimated from the available data).

<b>MedDRA system organ classes</b>	<b>Side effect</b>	<b>Frequency</b>
<u>Infections and infestations</u>	Nasopharyngitis	Common
<u>Blood and lymphatic system disorders</u>	Thrombocytopenia	Rare
<u>Immune system disorders</u>	Allergic reactions.	Common
	Anaphylaxis	Very rare
<u>Metabolism and nutrition disorders</u>	Hyperglycaemia	Common
	Hypoglycaemia, Weight gain, Anorexia	Uncommon
<u>Psychiatric disorders</u>	Nightmare, Insomnia	Uncommon
<u>Nervous system disorders</u>	Headache	Common
	Dizziness, Paraesthesia, Hypoesthesia, Dysgeusia, Amnesia	Uncommon
	Peripheral neuropathy	Rare
<u>Eye disorders</u>	Vision blurred	Uncommon
	Visual disturbance	Rare
<u>Ear and labyrinth disorders</u>	Tinnitus	Uncommon
	Hearing loss	Very rare
<u>Respiratory, thoracic and mediastinal disorders</u>	Pharyngolaryngeal pain, Epistaxis	Common
<u>Gastrointestinal disorders</u>	Constipation, Flatulence, Dyspepsia, Nausea, Diarrhoea	Common
	Vomiting, Abdominal pain upper and lower, Eructation, Pancreatitis	Uncommon
<u>Hepatobiliary disorders</u>	Hepatitis	Uncommon
	Cholestasis	Rare
	Hepatic failure	Very rare
<u>Skin and subcutaneous tissue disorders</u>	Urticaria, Skin rash, Pruritus, Alopecia	Uncommon
	Angioneurotic oedema, Dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome Toxic epidermal necrolysis	Rare
<u>Musculoskeletal and connective tissue disorders</u>	Myalgia,	Common

	Arthralgia, Pain in extremity, Muscle spasms, Joint swelling, Back pain	
	Neck pain, Muscle fatigue	Uncommon
	Myopathy, Myositis, Rhabdomyolysis Tendonopathy, sometimes complicated by rupture	Rare
	Lupus-like syndrome	Very rare
	Immune-mediated necrotising myopathy (see section 4.4)	Not known
<u>Reproductive system and breast disorders</u>	Gynecomastia	Very rare
<u>General disorders and administration site conditions</u>	Malaise, Asthenia, Chest pain, Peripheral oedema, Fatigue, Pyrexia	Uncommon
<u>Investigations</u>	Liver function test abnormal, Blood creatine kinase increased	Common
	White blood cells urine positive	Uncommon

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% of the patients on atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated creatine kinase (CK) levels greater than 3 times upper limit of normal occurred in 2.5% of the 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.).

#### Class Effects

The following adverse events have been reported with some statins:

- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
- Diabetes Mellitus: Frequency will depend on the presence or absence of risk factors (fasting blood glucose  $\geq 5.6$  mmol/L, BMI  $> 30 \text{ kg/m}^2$ , raised triglycerides, history of hypertension).

#### Paediatric population

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

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

## Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); e-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

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

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors,  
ATC code: C10AA05.

#### Mechanism of action

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

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

#### Pharmacodynamic effects

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

#### Clinical efficacy and safety

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

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

#### Homozygous familial hypercholesterolaemia

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

#### Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid- Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by

intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

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

In the atorvastatin group, LDL-C was reduced to a mean of 2.04 mmol/L +/-0.8 (78.9 mg/dl +/-30) from baseline 3.89 mmol/l +/-0.7 (150 mg/dl +/-28) and in the pravastatin group, LDL-C was reduced to a mean of 2.85 mmol/l +/-0.7 (110 mg/dl +/-26) from baseline 3.89 mmol/l +/-0.7 (150 mg/dl +/-26) (p<0.0001). Atorvastatin also significantly reduced mean TC by 34.1% (pravastatin: -18.4%, p<0.0001), mean TG levels by 20% (pravastatin: -6.8%, p<0.0009), and mean apolipoprotein B by 39.1% (pravastatin: -22%, p<0.0001). Atorvastatin increased mean HDL-C by 2.9% (pravastatin: +5.6%, p=NS). There was a 36.4% mean reduction in CRP in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).

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

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

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

#### Acute coronary syndrome

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

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

#### Prevention of cardiovascular disease

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

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

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

<b>Event</b>	<b>Relative Risk Reduction (%)</b>	<b>No. of Events (Atorvastatin vs Placebo)</b>	<b>Absolute Risk Reduction<sup>1</sup> (%)</b>	<b>p-value</b>
Fatal CHD plus nonfatal MI	36%	100 vs 154	1.1%	0.0005
Total cardiovascular events and revascularisation 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. There was significant treatment interaction by antihypertensive baseline therapy. The primary endpoint (fatal CHD plus non-fatal MI) was significantly reduced by atorvastatin in patients treated with Amlodipine (HR 0.47 (0.32-0.69),  $p=0.00008$ ), but not in those treated with Atenolol (HR 0.83 (0.59-1.17),  $p=0.287$ ).

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomised, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS), in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C  $\leq 4.14$  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:

	<b>Relative Risk Reduction (%)</b>	<b>No. of Events (Atorvastatin vs Placebo)</b>	<b>Absolute Risk Reduction<sup>1</sup> (%)</b>	<b>p-value</b>
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37%	83 vs 127	3.2%	0.0010
MI (fatal and nonfatal, AMI, 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 favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group,  $p=0.0592$ ).

#### Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischaemic 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 ischaemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%,  $p=0.01$ ) and increased the incidence of haemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%,  $p=0.02$ ) compared to placebo.

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

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

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

#### Paediatric population

##### *Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 6-17 years old*

An 8-week, open-label study to evaluate pharmacokinetics, pharmacodynamics, and safety and tolerability of atorvastatin was conducted in children and adolescents with genetically confirmed heterozygous familial hypercholesterolaemia 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 HeFH children 6-15 years of age were enrolled and treated with atorvastatin for up to three years. Inclusion in the study required confirmed HeFH and a baseline LDL-C level  $\geq$  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 ( $\pm$  SD) baseline LDL-C value was 6.12 (1.26) mmol/L which was approximately 233 (48) mg/dL. See table 3 below for final results.

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

**TABLE 3 Lipidlowering Effects of Atorvastatin in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia (mmol/L)**

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

TC = total cholesterol; LDLC = low density lipoprotein cholesterol; HDLC = high density lipoprotein cholesterol; TG = triglycerides; Apo B = apolipoprotein B; "Month 36/ET" included final visit data for subjects who ended participation prior to the scheduled 36 month timepoint as well as full 36 month data for subjects 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 Hypercholesterolaemia in Paediatric Patients aged 10-17 years old*

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

(n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level was >3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26-week double-blind phase.

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

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

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

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

## 5.2 Pharmacokinetic properties

### Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations ( $C_{max}$ ) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

### Distribution

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

### Biotransformation

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

### Elimination

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

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

### Special Populations

#### *Elderly*

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

#### *Paediatric population*

In an open-label, 8-week study, Tanner Stage 1 (N=15) and Tanner Stage  $\geq 2$  (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolaemia and baseline LDL-C  $\geq 4$  mmol/L were treated with 5 or 10 mg of chewable or 10



or 20 mg of film-coated atorvastatin tablets once daily, respectively. Body weight was the only significant covariate in atorvastatin population PK model. Apparent oral clearance of atorvastatin in paediatric subjects appeared similar to adults when scaled allometrically by body weight. Consistent decreases in LDL-C and TC were observed over the range of atorvastatin and o-hydroxyatorvastatin exposures.

#### *Gender*

Concentrations of atorvastatin and its active metabolites in women differ from those in men (women: approx. 20% higher for  $C_{max}$  and 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 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

#### *SLOC1B1 polymorphism:*

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

### **5.3 Preclinical safety data**

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

There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or foetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer.

In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **Tablet Core**

Silica, colloidal anhydrous  
Sodium carbonate  
Microcrystalline cellulose  
L-Arginine  
Lactose  
Croscarmellose sodium  
Hydroxypropyl cellulose  
Magnesium stearate

#### **Film-coat**

#### **Opadry AMB OY-B-28920 containing:**

Polyvinyl Alcohol  
Titanium dioxide (E171)  
Talc  
Soya lecithin

Xanthan gum (E415)

Or

**Opadry II 85F18378 containing:**

Polyvinyl Alcohol

Titanium dioxide (E171)

Talc

Macrogol

**6.2 Incompatibilities**

Not-applicable

**6.3 Shelf life**

OPA/Al/PVC/Al blisters and tablet container: 3 years

PVC/Aclar blisters: 2 years

Use within 3 months after the first opening of the tablet container.

**6.4 Special precautions for storage**

OPA/Al/PVC/Al blisters and tablet container: Store in the original package in order to protect from light and moisture.

PVC/Aclar blisters: Store in the original package in order to protect from moisture, keep the blister in the outer carton in order to protect from light.

**6.5 Nature and contents of container**

Opaque HDPE tablet container and PP closure containing 10, 14, 28, 30, 50, 56, 60, 90, 100, 200, 250 and 500 tablets.

PVC/Aclar (Aclar/PVC/Al) or (OPA/Al/PVC/Al) opaque blisters containing 10, 14, 28, 30, 50, 56, 60, 84, 90, 98 and 100 tablets, calendar packs of 28 tablets or multipacks containing 98 (2 packs of 49) tablets.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

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

**7 MARKETING AUTHORISATION HOLDER**

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate

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**8 MARKETING AUTHORISATION NUMBER**

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**10 DATE OF REVISION OF THE TEXT**

