Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lipitor 40mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40mg atorvastatin (as the calcium trihydrate salt)
Excipients: Lactose
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
Product imported from UK:
White, elliptical tablets debossed '40' on one side and 'PD 157' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypercholesterolaemia
Lipitor is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults 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.
Lipitor is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (eg. LDL apheresis) or if such treatments are unavailable.

Prevention of Cardiovascular Disease
Prevention of cardiovascular events in 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.
Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

4.2 Posology and method of administration

The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor and should continue on this diet during treatment with Lipitor. The usual starting dose is 10 mg once a day. Doses should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. Doses may be given at any time of day with or without food.

Current consensus guidelines should be consulted to establish treatment goals for individual patients
Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia
The majority of patients are controlled with 10 mg Lipitor once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous Familial Hypercholesterolaemia
Patients should be started with Lipitor 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 Lipitor.

Homozygous Familial Hypercholesterolaemia
In a compassionate-use study of 64 patients with confirmed homozygous familial hypercholesterolaemia, the mean reduction in LDL-C was approximately 21% when Lipitor was administered at doses up to 80 mg/day.

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.

Dosage in Patients With Renal Insufficiency
Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required.

Dosage in Patients with Hepatic Dysfunction
In patients with moderate to severe hepatic dysfunction, the therapeutic response to Lipitor is unaffected but exposure to the drug is greatly increased. Cmax increases by approximately 16 fold and AUC (0-24) by approximately 11 fold. Therefore, caution should be exercised in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Geriatric Use
Efficacy and safety in patients older than 70 using recommended doses is similar to that seen in the general population.

Paediatric use
Paediatric use should only be carried out by specialists.
Experience in paediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidaemias, such as homozygous familial hypercholesterolaemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability.

Developmental safety data in this population have not been evaluated

4.3 Contraindications

Lipitor is contra-indicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, myopathy, during pregnancy, while breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures.

4.4 Special warnings and precautions for use

Liver Effects
As with other lipid lowering agents including HMG-CoA reductase inhibitors and non-absorbable bile acid-binding resins, increases in liver enzymes have occurred during therapy with Lipitor. The significance of these changes, which usually appears during the first few months of treatment, is not known.
It is recommended that liver function tests be performed before the initiation of treatment, at 12 weeks after initiation of therapy or elevation of dose and periodically (eg six monthly) 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) resolves. Should an increase in transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended (See 4.8 Adverse Effects).

Lipitor 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 CHD who had a recent stroke or 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).

Muscle Effects

Treatment with HMG-CoA reductase inhibitors (statins) has been associated with the onset of myalgia, myopathy, and very rarely rhabdomyolysis. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness or muscle cramps. In such cases creatine kinase (CK) levels should be measured (see below).

Before Treatment

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

In such situations, the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended.

If CPK levels are significantly elevated (>5 times ULN) at baseline, treatment should not be started.

Creatine phosphokinase measurement

Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK 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

- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK 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 CPK levels are elevated to 5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK 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.

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivates or HIV-protease inhibitors. The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, a lower starting dose of atorvastatin is recommended. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be considered (see Section 4.5).

As with other drugs in this class, rhabdomyolysis with acute renal failure, has been reported. Lipitor therapy should be temporarily withheld or discontinued in any patient having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, (eg: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electolyte disorders, and uncontrolled seizures).

Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medication.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with Lipitor, as with other drugs in this class is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics, azole antifungals, HIV-protease inhibitors or niacin. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, a lower starting dose of atorvastatin is recommended. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be considered and clinical monitoring of these patients is recommended (see Section 4.4).

Inhibitors of cytochrome P450 3A4:
Atorvastatin is metabolized by cytochrome P450 3A4.
Interaction may occur when Lipitor is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see Section 4.4).

In vitro studies indicate that atorvastatin is a weak inhibitor of cytochrome P450 3A4.
In clinical studies in which Lipitor was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

Transporter Inhibitors: Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in a 7.7 fold increase in exposure to atorvastatin. In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg

Erythromycin, clarithromycin: Erythromycin and clarithromycin are known inhibitors of cytochrome P450 3A4. Co-administration ofatorvastatin 80mg OD and erythromycin (500 mg QID) resulted in a 33% increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10mg OD and clarithromycin (500 mg BID) resulted in a 3.4 fold increase in exposure to atorvastatin. In cases where co-administration of clarithromycin with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.

Itraconazole: Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 1.5-2.3 fold increase in exposure to atorvastatin. In cases where co-administration of itraconazole with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.

Protease inhibitors: Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with an approximately two-fold increase in plasma concentrations of atorvastatin. Consideration should be given to starting atorvastatin at a lower dose (see section 4.2) when co-administered with a protease inhibitor

Diltiazem hydrochloride: Co-administration of diltiazem 240 mg with atorvastatin 40 mg resulted in a 51% increase in exposure to atorvastatin. After initiation of diltiazem or following dosage adjustments, clinical monitoring of these patients is recommended.

Ezetimibe: The use of ezetimibe alone is associated with myopathy. The risk of myopathy may therefore be increased with concomitant use of ezetimibe and atorvastatin.

Grapefruit juice: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active orthohydroxy metabolite.

However, large quantities of grapefruit juice (over 1.2L 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. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.
Inducers of cytochrome P450 3A4: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg 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 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1) simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Verapamil and Amiodarone: Interaction studies with verapamil and amiodarone have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin.

Azithromycin: Co-administration of Lipitor (10 mg OD) and azithromycin (500 mg OD) did not alter the plasma concentrations of atorvastatin.

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

Oral contraceptives: Administration of Lipitor with an oral contraceptive containing norethisterone and ethinyl oestradiol produced increases in plasma concentrations of norethisterone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Amlodipine: In a drug-drug interaction study in healthy subjects, co-administration of atorvastatin 80 mg and amlodipine 10 mg resulted in an 18% increase in exposure to atorvastatin.

Gemfibrozil/ fibric acid derivatives:The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse event has been described when fibrates are co-administered with HMG-CoA reductase inhibitors. The risk of atorvastatin induced myopathy may therefore be increased with concomitant use of fibric acid derivatives.. Co-administration of atorvastatin with fibrates (especially gemfibrozil) should only be undertaken with caution. (see Section 4.4)

Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in exposure to atorvastatin.
Antacid: Co-administration of Lipitor with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approximately 35%; however, LDL-C reduction was not altered.

Warfarin: Co-administration of Lipitor and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.
Cimetidine: An interaction study with cimetidine and Lipitor was conducted, and no interaction was seen.

4.6 Fertility, pregnancy and lactation

Lipitor is contra-indicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

An interval of 1 month should be allowed from stopping Lipitor treatment to conception in the event of planning a pregnancy.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

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

4.7 Effects on ability to drive and use machines

There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

4.8 Undesirable effects

Lipitor is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to Lipitor.

The most frequent (1% or more) adverse effects associated with Lipitor therapy, in patients participating in controlled clinical studies were:
Nervous System Disorders: headache
General Disorders and Administration Site Conditions: asthenia
Gastrointestinal Disorders: abdominal pain, dyspepsia, nausea, flatulence, constipation, diarrhoea
Psychiatric Disorders: insomnia
Musculoskeletal and Connective Tissue Disorders: myalgia

As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Lipitor. 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 approximately 0.7% of patients on Lipitor. The incidence of these abnormalities was 0.2%, 0.2%, 0.6% and 2.3% for 10, 20, 40 and 80mg, respectively. These elevations were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Lipitor, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Lipitor-treated patients. Of these patients 0.1% had concurrent muscle pain, tenderness, or weakness.

Additional adverse events that have been reported in atorvastatin clinical trials are categorised below according to system organ class and frequency. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%) and very rare (<0.01%).

Metabolism and Nutrition Disorders	Anorexia	uncommon
	hypoglycaemia	very rare
	hyperglycaemia	very rare
Nervous system disorders	dizziness	common
	paraesthesia	uncommon
	peripheral neuropathy	rare
Gastrointestinal Disorders	Vomiting	uncommon
	pancreatitis	rare
Hepatobiliary Disorders	Hepatitis	very rare

	cholestatic jaundice	very rare
Skin and Subcutaneous Tissue Disorders	Alopecia	uncommon
	Pruritis	uncommon
	Rash	uncommon
Musculoskeletal and Connective Tissue Disorder	muscle cramps	uncommon
	Myositis	rare
	myopathy	very rare
Reproductive System and Breast Disorders	impotence	uncommon
General Disorders and Administration Site Conditions	chest pain	common
	Angina	common
	angioneurotic oedema	very rare

Post-marketing surveillance

Adverse events that have been reported post-marketing which are not listed above :

Blood and Lymphatic System Disorders	thrombocytopenia	uncommon
Immune System Disorders	allergic reactions (including anaphylaxis)	common
Metabolism and Nutrition Disorders	weight gain	uncommon
Nervous System Disorders	hypoesthesia	common
	Amnesia	uncommon
	dysgeusia	very rare
Hepatobillary disorders	hepatic failure	very rare
Eye disorders	Visual disturbances	very rare
Ear and Labyrinth Disorders	Tinnitus	uncommon
	Hearing loss	very rare
Skin and Subcutaneous Tissue Disorders	bullous rashes	rare
	erythema	very rare
	multiforme	
	Stevens-Johnson syndrome	very rare
Musculoskeletal and Connective Tissue Disorders	arthralgia	common

	back pain	common
	rhabdomyolysis (see section 4.4)	very rare
	tendon rupture	
Reproductive System and Breast Disorders	gynaecomastia	very rare
General Disorders and Administration Site Conditions	Malaise	uncommon
	peripheral oedema	rare
	Fatigue	common

The following adverse events have been reported with some statins:
• Sleep disturbances, including insomnia and nightmares.
• Memory loss.
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see Section 4.4).

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 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 high affinity LDL receptor.

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

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

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides in a dose related manner. Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and

reduces the LDL/HDL and total cholesterol/HDL ratios.

These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

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

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In 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 atovastatin were statistically significant (p=0.02). There was a 36.4% mean reduction in c-reactive protein (CRP) in the atorvastatin group compared to a 5.2% reduction in the pravastatin group (p<0.0001).
The safety and tolerability profiles of the two treatment groups were comparable.

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 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 ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).
The absolute and relative risk reduction effect of atorvastatin was as follows:

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

Total coronary events	29 %	178 vs. 247	1.4%	0.0006

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

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

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

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

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

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

[1]Based on difference in crude events rates occurring over a median follow-up of 3.9 years.
AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CHD = coronary heart disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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

Recurrent Stroke
In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 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 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 post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.02) 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, 1.71-14.6), 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.

5.2 Pharmacokinetic properties

Pharmacokinetics and Drug Metabolism
Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

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

Metabolism: 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 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.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug 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.

Special Populations
Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
Paediatric: Pharmacokinetic data in the paediatric population are not available.
Gender: Concentrations of atorvastatin and its active metabolites in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased

(approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on AUC(0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC (0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Calcium carbonate
Microcrystalline cellulose
Lactose
Croscarmellose sodium
Polysorbate 80
Hyprolose
Magnesium stearate

Tablet Coating:
Hypromellose
Macrogol 8000
Titanium dioxide (E171)
Talc
Simeticone
Macrogol stearate
Sorbic acid
Candelilla wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Foil/foil blisters in an over-labelled carton containing 28 tablets (calendar pack), consisting of a polyamide/aluminium foil/polyvinyl chloride unit-dose blister and a paper/polyester/aluminium foil/vinyl heat-seal coated backing or an aluminium foil/vinyl heat-seal coated backing.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

McDowell Pharmaceuticals
4 Altona Road
Lisburn
N.Ireland BT27 5QB

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1473/2/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 9th January 2009

10 DATE OF REVISION OF THE TEXT

November 2010