



Public Assessment Report

Decentralised Procedure

**ATORVASTATIN 10MG FILM-COATED TABLETS
ATORVASTATIN 20MG FILM-COATED TABLETS
ATORVASTATIN 40MG FILM-COATED TABLETS
ATORVASTATIN 80MG FILM-COATED TABLETS**

Procedure No: UK/H/2900/001-4/DC

UK Licence No: PL 00289/1289-92

TEVA UK LIMITED

LAY SUMMARY

MHRA approved licences for the medicines Atorvastatin Tablets on 3 August 2010. These medicines are available in a range of strengths, containing 10mg, 20mg, 40mg and 80mg of the active ingredient, atorvastatin. The licences were granted to Teva UK Limited. This company is responsible for marketing the product in the UK.

Atorvastatin belongs to a group of medicines called statins, which are lipid (fat) regulating medicines.

Atorvastatin is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and lifestyle changes on their own have failed. If you are at an increased risk of heart disease, atorvastatin can also be used to reduce such risk even if your cholesterol levels are normal. A standard cholesterol lowering diet should be continued during treatment.

Cholesterol is a naturally occurring substance in the body necessary for normal growth. However, if there is too much cholesterol in your blood it can be deposited on the walls of the blood vessels, which may eventually become blocked. This is one of the most common causes of heart disease. It is accepted that raised cholesterol levels increase the risk of heart disease. Other factors include high blood pressure, diabetes, increased weight, lack of exercise, smoking, or a family history of heart disease.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Atorvastatin Tablets outweigh the risks, hence Marketing Authorisations have been granted.

TABLE OF CONTENTS

Module 1: Information about initial procedure	Page 4
Module 2: Summary of Product Characteristics	Page 5
Module 3: Product Information Leaflets	Page 49
Module 4: Labelling	Page 51
Module 5: Scientific Discussion	Page 55
1 Introduction	
2 Quality aspects	
3 Non-clinical aspects	
4 Clinical aspects	
5 Overall conclusions	
Module 6 Steps taken after initial procedure	Page 63

Module 1

Product Name	Atorvastatin 10mg, 20mg, 40mg and 80mg Film-Coated Tablets
Type of Application	Generic, Article 10.1
Active Substances	Atorvastatin
Form	Tablet
Strength	10, 20, 40 and 80mg Tablets
MA Holder	TEVA UK Ltd, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK
Reference Member State (RMS)	UK
CMS	UK/H/2900/001-4/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia
Procedure Number	UK/H2900/001-4/DC
Timetable	Day 210 – 05 July 2010

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 9.7 mm x 5.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients 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 non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in patients 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 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

For oral administration.

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

Dosage 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 dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 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

In a compassionate-use study of 64 patients there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21%. Atorvastatin was administered at doses up to 80 mg/day.

The dosage of atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily. 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.

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations or lipid effects of atorvastatin; thus, no adjustment of dose is required.

Dosage in patients with impaired liver function

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

Elderly

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. In this population the recommended starting dose is 10 mg of atorvastatin per day. Doses above 20mg/day have not been investigated in patients aged <18 years. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (ULN)
- with myopathy
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment or dose incrementation and periodically thereafter (e.g. every six months). 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 persist, atorvastatin should be discontinued (see section 4.8).

Moderate (< 3x ULN) elevation of serum transaminases have been reported following therapy with statins. These changes appeared soon after initiation of therapy, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Atorvastatin 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 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).

Skeletal muscle effects

Atorvastatin may on 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 CPK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

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 the elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other pre-disposing 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 re-measured 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 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 the CPK levels are elevated to ≤ 5 x 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.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (>10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

The risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain agents that may increase the plasma concentration of atorvastatin such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivatives 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 agents. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used. Such patients should be closely clinically monitored (see section 4.5).

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.

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

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

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, HIV protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully weighed. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and section 4.2). Such patients should be closely clinically monitored (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Interaction may occur when atorvastatin 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 agents (see section 4.4).

Transporter inhibitors

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in a 7.7-fold increase in atorvastatin exposure. 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 of atorvastatin 80 mg once daily and erythromycin 500 mg four times daily resulted in a 33% increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10 mg once daily and clarithromycin 500 mg twice daily resulted in a 3.4-fold increase in atorvastatin exposure. In cases where concomitant treatment with clarithromycin and atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Itraconazole

Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 1.5 to 2.3-fold increase in atorvastatin exposure. In cases where co-administration of itraconazole with atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin exposure. Such patients should be clinically monitored after initiation of diltiazem or following dosage adjustment.

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

Large quantities of grapefruit juice (over 1.2 L daily for 5 days) increased the AUC of atorvastatin 2.5-fold and the 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, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) can lead to variable reductions in plasma concentrations of atorvastatin. This decrease may achieve a maximal value of 80% with rifampicin. Cholesterol levels should be monitored in order to ensure efficacy.

Verapamil

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

Other concomitant therapy

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see section 4.4).

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. 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. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) 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.

Antacid

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approximately 35%; however, LDL-C reduction was not altered.

Warfarin

Co-administration of atorvastatin and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Other

In clinical studies in which atorvastatin was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential must use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not been established (see section 4.3).

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 medicinal product or its metabolites are excreted in human milk (see section 5.3).

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

The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment.

Less than 2% of patients were discontinued from clinical trials due to adverse events attributed to atorvastatin.

Based on data from clinical studies and extensive post-marketing experience, the following paragraphs present the adverse event profile for atorvastatin.

Estimated frequencies of events are ranked according to the following convention: very common ($\geq 1/10$); 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 ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Common: allergic reactions

Very rare: anaphylaxis

Metabolism and nutrition disorders

Uncommon: hyperglycaemia, hypoglycaemia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, paraesthesia, hypoaesthesia

Uncommon: peripheral neuropathy, amnesia

Very rare: dysgeusia

Eye disorders

Very rare: visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: anorexia, vomiting, pancreatitis

Skin and subcutaneous tissue disorders

Common: skin rash, pruritus

Uncommon: urticaria, alopecia

Rare: bullous rashes (including erythema multiforme)

Very rare: angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia

Uncommon: myopathy

Rare: myositis, rhabdomyolysis, muscle cramps

Very rare: tendinopathy sometimes complicated by rupture

General disorders

Common: asthenia, chest pain, back pain, peripheral oedema, fatigue
 Uncommon: malaise, weight gain

Hepatobiliary disorders

Rare: hepatitis, cholestatic jaundice
 Very rare: hepatic failure

Reproductive system and breast disorders

Uncommon: impotence
 Very rare: gynaecomastia

Investigations

Elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose-related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins: sleep disturbances including nightmares, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

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 CPK 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: HMG-CoA reductase inhibitors
 ATC code: C10A-A05

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

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 agents.

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial 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 the risk for cardiovascular events and cardiovascular mortality.

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 predefined 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 antihypertensive 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

¹Based 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, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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)	42%	38 vs. 64	1.9%	0.0070

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
AMI, silent MI)				
Strokes (fatal and non-fatal)	48%	21 vs 39	1.3%	0.0163

¹Based 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 4,731 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% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a *post-hoc* analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, p=0.01) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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.

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.

Metabolism

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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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

- Elderly: 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 from those in men (women: approximately 20% higher for C_{max} and approximately 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 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 C_{max} and approximately 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*

Microcrystalline cellulose
Sodium carbonate anhydrous
Maltose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Hydroxypropylcellulose
Triethyl citrate (E1505)
Polysorbate 80
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Aluminium-aluminium blisters.

Atorvastatin 10 mg Film-coated Tablets are available in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1289

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

03/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin 20 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 20 mg atorvastatin (as atorvastatin calcium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 12.5 mm x 6.6 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****Hypercholesterolaemia**

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients 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 non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in patients 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 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

For oral administration.

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

Dosage 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 dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 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

In a compassionate-use study of 64 patients there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21%. Atorvastatin was administered at doses up to 80 mg/day.

The dosage of atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily. 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.

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations or lipid effects of atorvastatin; thus, no adjustment of dose is required.

Dosage in patients with impaired liver function

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

Elderly

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. In this population the recommended starting dose is 10 mg of atorvastatin per day. Doses above 20mg/day have not been investigated in patients aged <18 years. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (ULN)
- with myopathy
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment or dose incrementation and periodically thereafter (e.g. every six months). 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 persist, atorvastatin should be discontinued (see section 4.8).

Moderate (< 3x ULN) elevation of serum transaminases have been reported following therapy with statins. These changes appeared soon after initiation of therapy, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Atorvastatin 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 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).

Skeletal muscle effects

Atorvastatin may on 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 CPK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

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 the elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other pre-disposing 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 re-measured 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 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 the CPK levels are elevated to ≤ 5 x 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.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (>10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

The risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain agents that may increase the plasma concentration of atorvastatin such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivatives 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 agents. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used. Such patients should be closely clinically monitored (see section 4.5).

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.

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

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

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, HIV protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully weighed. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and section 4.2). Such patients should be closely clinically monitored (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Interaction may occur when atorvastatin 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 agents (see section 4.4).

Transporter inhibitors

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in a 7.7-fold increase in atorvastatin exposure. 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 of atorvastatin 80 mg once daily and erythromycin 500 mg four times daily resulted in a 33% increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10 mg once daily and clarithromycin 500 mg twice daily resulted in a 3.4-fold increase in atorvastatin exposure. In cases where concomitant treatment with clarithromycin and atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Itraconazole

Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 1.5 to 2.3-fold increase in atorvastatin exposure. In cases where co-administration of itraconazole with atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin exposure. Such patients should be clinically monitored after initiation of diltiazem or following dosage adjustment.

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

Large quantities of grapefruit juice (over 1.2 L daily for 5 days) increased the AUC of atorvastatin 2.5-fold and the 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, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) can lead to variable reductions in plasma concentrations of atorvastatin. This decrease may achieve a maximal value of 80% with rifampicin. Cholesterol levels should be monitored in order to ensure efficacy.

Verapamil

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

Other concomitant therapy

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see section 4.4).

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. 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. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) 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.

Antacid

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approximately 35%; however, LDL-C reduction was not altered.

Warfarin

Co-administration of atorvastatin and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Other

In clinical studies in which atorvastatin was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential must use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not been established (see section 4.3).

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 medicinal product or its metabolites are excreted in human milk (see section 5.3).

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

The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment.

Less than 2% of patients were discontinued from clinical trials due to adverse events attributed to atorvastatin.

Based on data from clinical studies and extensive post-marketing experience, the following paragraphs present the adverse event profile for atorvastatin.

Estimated frequencies of events are ranked according to the following convention: very common ($\geq 1/10$); 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 ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Common: allergic reactions

Very rare: anaphylaxis

Metabolism and nutrition disorders

Uncommon: hyperglycaemia, hypoglycaemia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, paraesthesia, hypoaesthesia

Uncommon: peripheral neuropathy, amnesia

Very rare: dysgeusia

Eye disorders

Very rare: visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: anorexia, vomiting, pancreatitis

Skin and subcutaneous tissue disorders

Common: skin rash, pruritus

Uncommon: urticaria, alopecia

Rare: bullous rashes (including erythema multiforme)

Very rare: angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia

Uncommon: myopathy

Rare: myositis, rhabdomyolysis, muscle cramps

Very rare: tendinopathy sometimes complicated by rupture

General disorders

Common: asthenia, chest pain, back pain, peripheral oedema, fatigue

Uncommon: malaise, weight gain

Hepatobiliary disorders

Rare: hepatitis, cholestatic jaundice

Very rare: hepatic failure

Reproductive system and breast disorders

Uncommon: impotence

Very rare: gynaecomastia

Investigations

Elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose-related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins: sleep disturbances including nightmares, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

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 CPK 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: HMG-CoA reductase inhibitors

ATC code: C10A-A05

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

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 agents.

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial 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 the risk for cardiovascular events and cardiovascular mortality.

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 predefined 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 antihypertensive 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

¹Based 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, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina,	37%	83 vs. 127	3.2%	0.0010

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
CABG, PTCA, revascularisation, stroke)				
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

¹Based 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 4,731 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% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a *post-hoc* analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, p=0.01) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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.

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.

Metabolism

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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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

- Elderly: 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 from those in men (women: approximately 20% higher for C_{max} and approximately 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 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 C_{max} and approximately 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*

Microcrystalline cellulose
Sodium carbonate anhydrous
Maltose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Hydroxypropylcellulose
Triethyl citrate (E1505)
Polysorbate 80
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Aluminium-aluminium blisters.

Atorvastatin 20 mg Film-coated Tablets are available in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited

Brampton Road,

Hampden Park,

Eastbourne,

East Sussex BN22 9AG

UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1290

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

03/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin 40 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 40 mg atorvastatin (as atorvastatin calcium)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 15.6 mm x 8.3 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****Hypercholesterolaemia**

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients 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 non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in patients 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 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

For oral administration.

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

Dosage 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 dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 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

In a compassionate-use study of 64 patients there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21%. Atorvastatin was administered at doses up to 80 mg/day.

The dosage of atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily. 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.

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations or lipid effects of atorvastatin; thus, no adjustment of dose is required.

Dosage in patients with impaired liver function

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

Elderly

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. In this population the recommended starting dose is 10 mg of atorvastatin per day. Doses above 20mg/day have not been investigated in patients aged <18 years. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (ULN)
- with myopathy
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment or dose incrementation and periodically thereafter (e.g. every six months). 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 persist, atorvastatin should be discontinued (see section 4.8).

Moderate (< 3x ULN) elevation of serum transaminases have been reported following therapy with statins. These changes appeared soon after initiation of therapy, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Atorvastatin 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 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).

Skeletal muscle effects

Atorvastatin may on 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 CPK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

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 the elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other pre-disposing 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 re-measured 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 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 the CPK levels are elevated to ≤ 5 x 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.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (>10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

The risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain agents that may increase the plasma concentration of atorvastatin such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivatives 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 agents. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used. Such patients should be closely clinically monitored (see section 4.5).

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.

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

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

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, HIV protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully weighed. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and section 4.2). Such patients should be closely clinically monitored (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Interaction may occur when atorvastatin 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 agents (see section 4.4).

Transporter inhibitors

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in a 7.7-fold increase in atorvastatin exposure. 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 of atorvastatin 80 mg once daily and erythromycin 500 mg four times daily resulted in a 33% increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10 mg once daily and clarithromycin 500 mg twice daily resulted in a 3.4-fold increase in atorvastatin exposure. In cases where concomitant treatment with clarithromycin and atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Itraconazole

Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 1.5 to 2.3-fold increase in atorvastatin exposure. In cases where co-administration of itraconazole with atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin exposure. Such patients should be clinically monitored after initiation of diltiazem or following dosage adjustment.

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

Large quantities of grapefruit juice (over 1.2 L daily for 5 days) increased the AUC of atorvastatin 2.5-fold and the 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, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) can lead to variable reductions in plasma concentrations of atorvastatin. This decrease may achieve a maximal value of 80% with rifampicin. Cholesterol levels should be monitored in order to ensure efficacy.

Verapamil

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

Other concomitant therapy

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see section 4.4).

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. 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. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) 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.

Antacid

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approximately 35%; however, LDL-C reduction was not altered.

Warfarin

Co-administration of atorvastatin and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Other

In clinical studies in which atorvastatin was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential must use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not been established (see section 4.3).

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 medicinal product or its metabolites are excreted in human milk (see section 5.3).

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

The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment.

Less than 2% of patients were discontinued from clinical trials due to adverse events attributed to atorvastatin.

Based on data from clinical studies and extensive post-marketing experience, the following paragraphs present the adverse event profile for atorvastatin.

Estimated frequencies of events are ranked according to the following convention: very common ($\geq 1/10$); 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 ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Common: allergic reactions

Very rare: anaphylaxis

Metabolism and nutrition disorders

Uncommon: hyperglycaemia, hypoglycaemia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, paraesthesia, hypoaesthesia

Uncommon: peripheral neuropathy, amnesia

Very rare: dysgeusia

Eye disorders

Very rare: visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: anorexia, vomiting, pancreatitis

Skin and subcutaneous tissue disorders

Common: skin rash, pruritus

Uncommon: urticaria, alopecia

Rare: bullous rashes (including erythema multiforme)

Very rare: angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia

Uncommon: myopathy

Rare: myositis, rhabdomyolysis, muscle cramps

Very rare: tendinopathy sometimes complicated by rupture

General disorders

Common: asthenia, chest pain, back pain, peripheral oedema, fatigue

Uncommon: malaise, weight gain

Hepatobiliary disorders

Rare: hepatitis, cholestatic jaundice

Very rare: hepatic failure

Reproductive system and breast disorders

Uncommon: impotence

Very rare: gynaecomastia

Investigations

Elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose-related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins: sleep disturbances including nightmares, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

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 CPK 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: HMG-CoA reductase inhibitors

ATC code: C10A-A05

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

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 agents.

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial 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 the risk for cardiovascular events and cardiovascular mortality.

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 predefined 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 antihypertensive 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

¹Based 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, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

¹Based 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 4,731 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% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a *post-hoc* analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, $p=0.01$) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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.

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.

Metabolism

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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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

- Elderly: 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 from those in men (women: approximately 20% higher for C_{max} and approximately 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 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 C_{max} and approximately 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*

Microcrystalline cellulose
Sodium carbonate anhydrous
Maltose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Hydroxypropylcellulose
Triethyl citrate (E1505)
Polysorbate 80
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Aluminium-aluminium blisters.

Atorvastatin 40 mg Film-coated Tablets are available in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1291

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

03/08/2010

1 NAME OF THE MEDICINAL PRODUCT

Atorvastatin 80 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 80 mg atorvastatin (as atorvastatin calcium).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 18.8 mm x 10.3 mm.

4 CLINICAL PARTICULARS**4.1 Therapeutic indications****Hypercholesterolaemia**

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients 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 non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in patients 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 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

For oral administration.

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

Dosage 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 dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with atorvastatin 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

In a compassionate-use study of 64 patients there were 46 patients for whom confirmed LDL receptor information was available. From these 46 patients, the mean percent reduction in LDL-C was approximately 21%. Atorvastatin was administered at doses up to 80 mg/day.

The dosage of atorvastatin in patients with homozygous familial hypercholesterolaemia is 10 to 80 mg daily. 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.

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations or lipid effects of atorvastatin; thus, no adjustment of dose is required.

Dosage in patients with impaired liver function

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

Elderly

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. In this population the recommended starting dose is 10 mg of atorvastatin per day. Doses above 20mg/day have not been investigated in patients aged <18 years. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

Atorvastatin is contraindicated in patients:

- with hypersensitivity to the active substance or to any of the excipients
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal (ULN)
- with myopathy
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

Liver function tests should be performed before the initiation of treatment or dose incrementation and periodically thereafter (e.g. every six months). 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 persist, atorvastatin should be discontinued (see section 4.8).

Moderate (< 3x ULN) elevation of serum transaminases have been reported following therapy with statins. These changes appeared soon after initiation of therapy, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Atorvastatin 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 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).

Skeletal muscle effects

Atorvastatin may on 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 CPK levels (>10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

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 the elderly (age >70 years), the necessity of such measurement should be considered, according to the presence of other pre-disposing 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 re-measured 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 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 the CPK levels are elevated to ≤ 5 x 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.
- Atorvastatin must be discontinued if clinically significant elevation of CPK levels (>10 x ULN) occur, or if rhabdomyolysis is diagnosed or suspected.

The risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain agents that may increase the plasma concentration of atorvastatin such as ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivatives 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 agents. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used. Such patients should be closely clinically monitored (see section 4.5).

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.

In patients aged <18 years efficacy and safety have not been studied for treatment periods >52 weeks' duration and effects on long-term cardiovascular outcomes are unknown.

The effects of atorvastatin in children aged <10 years and premenarchal girls have not been investigated.

Long term effects on cognitive development, growth and pubertal maturation are unknown.

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

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, HIV protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these agents with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully weighed. A lower starting dose of atorvastatin is recommended for patients receiving other agents which may increase the plasma concentration of atorvastatin. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and section 4.2). Such patients should be closely clinically monitored (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolised by cytochrome P450 3A4. Interaction may occur when atorvastatin 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 agents (see section 4.4).

Transporter inhibitors

Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in a 7.7-fold increase in atorvastatin exposure. 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 of atorvastatin 80 mg once daily and erythromycin 500 mg four times daily resulted in a 33% increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10 mg once daily and clarithromycin 500 mg twice daily resulted in a 3.4-fold increase in atorvastatin exposure. In cases where concomitant treatment with clarithromycin and atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Itraconazole

Concomitant administration of atorvastatin 20 to 40 mg and itraconazole 200 mg daily resulted in a 1.5 to 2.3-fold increase in atorvastatin exposure. In cases where co-administration of itraconazole with atorvastatin is necessary, lower starting doses of atorvastatin are recommended. Patients requiring doses greater than 40 mg should be clinically monitored.

Protease inhibitors

Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin.

Diltiazem hydrochloride

Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin exposure. Such patients should be clinically monitored after initiation of diltiazem or following dosage adjustment.

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

Large quantities of grapefruit juice (over 1.2 L daily for 5 days) increased the AUC of atorvastatin 2.5-fold and the 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, rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) can lead to variable reductions in plasma concentrations of atorvastatin. This decrease may achieve a maximal value of 80% with rifampicin. Cholesterol levels should be monitored in order to ensure efficacy.

Verapamil

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

Other concomitant therapy

Gemfibrozil / fibric acid derivatives

The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see section 4.4).

Digoxin

When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. 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. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol

Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) 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.

Antacid

Co-administration of atorvastatin with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites by approximately 35%; however, LDL-C reduction was not altered.

Warfarin

Co-administration of atorvastatin and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of atorvastatin treatment. Nevertheless, patients receiving warfarin should be closely monitored when atorvastatin is added to their therapy.

Other

In clinical studies in which atorvastatin was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

Atorvastatin is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential must use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not been established (see section 4.3).

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 medicinal product or its metabolites are excreted in human milk (see section 5.3).

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

The most commonly expected adverse events are mainly gastrointestinal, including constipation, flatulence, dyspepsia, abdominal pain and usually ameliorate on continued treatment.

Less than 2% of patients were discontinued from clinical trials due to adverse events attributed to atorvastatin.

Based on data from clinical studies and extensive post-marketing experience, the following paragraphs present the adverse event profile for atorvastatin.

Estimated frequencies of events are ranked according to the following convention: very common ($\geq 1/10$); 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 ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Uncommon: thrombocytopenia

Immune system disorders

Common: allergic reactions

Very rare: anaphylaxis

Metabolism and nutrition disorders

Uncommon: hyperglycaemia, hypoglycaemia

Psychiatric disorders

Common: insomnia

Nervous system disorders

Common: headache, dizziness, paraesthesia, hypoaesthesia

Uncommon: peripheral neuropathy, amnesia

Very rare: dysgeusia

Eye disorders

Very rare: visual disturbance

Ear and labyrinth disorders

Uncommon: tinnitus

Very rare: hearing loss

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea

Uncommon: anorexia, vomiting, pancreatitis

Skin and subcutaneous tissue disorders

Common: skin rash, pruritus

Uncommon: urticaria, alopecia

Rare: bullous rashes (including erythema multiforme)

Very rare: angioneurotic oedema, Stevens-Johnson syndrome and toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders

Common: myalgia, arthralgia

Uncommon: myopathy

Rare: myositis, rhabdomyolysis, muscle cramps

Very rare: tendinopathy sometimes complicated by rupture

General disorders

Common: asthenia, chest pain, back pain, peripheral oedema, fatigue

Uncommon: malaise, weight gain

Hepatobiliary disorders

Rare: hepatitis, cholestatic jaundice

Very rare: hepatic failure

Reproductive system and breast disorders

Uncommon: impotence

Very rare: gynaecomastia

Investigations

Elevated serum transaminases have been reported in patients receiving atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (>3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on atorvastatin. These elevations were dose-related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on atorvastatin. Levels above 10 times the normal upper range occurred in 0.4% atorvastatin-treated patients (see section 4.4).

The following adverse events have been reported with some statins: sleep disturbances including nightmares, memory loss, sexual dysfunction, depression and exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

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 CPK 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: HMG-CoA reductase inhibitors

ATC code: C10A-A05

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

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 agents.

Atorvastatin has been shown to reduce concentrations of total-C (30%-46%), LDL-C (41%-61%), apolipoprotein B (34%-50%), and triglycerides (14%-33%) while producing variable increases in HDL-C and apolipoprotein A1 in a dose-response study. These results are consistent in patients with heterozygous familial hypercholesterolaemia, non-familial 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 the risk for cardiovascular events and cardiovascular mortality.

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 predefined 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 antihypertensive 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

¹Based 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, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤ 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:

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
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

<i>Event</i>	<i>Relative risk reduction (%)</i>	<i>No. of events (atorvastatin vs placebo)</i>	<i>Absolute risk reduction¹ (%)</i>	<i>P value</i>
Strokes (fatal and non-fatal)	48%	21 vs 39	1.3%	0.0163

¹Based 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 4,731 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% (216/2,365) for atorvastatin versus 8.9% (211/2,366) for placebo.

In a *post-hoc* analysis, atorvastatin 80 mg reduced the incidence of ischaemic stroke (218/2,365, 9.2% vs. 274/2,366, 11.6%, $p=0.01$) and increased the incidence of haemorrhagic stroke (55/2,365, 2.3% vs. 33/2,366, 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.

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.

Metabolism

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.

Excretion

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the medicinal product 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

- Elderly: 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 from those in men (women: approximately 20% higher for C_{max} and approximately 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 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 C_{max} and approximately 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

Microcrystalline cellulose
Sodium carbonate anhydrous
Maltose
Croscarmellose sodium
Magnesium stearate

Film-coating

Hypromellose (E464)
Hydroxypropylcellulose
Triethyl citrate (E1505)
Polysorbate 80
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Aluminium-aluminium blisters.

Atorvastatin 80 mg Film-coated Tablets are available in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited

Brampton Road,

Hampden Park,

Eastbourne,

East Sussex BN22 9AG

UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1292

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/08/2010

10 DATE OF REVISION OF THE TEXT

03/08/2010

Module 3

ATORVASTATIN 10 mg, 20 mg, 40 mg and 80 mg FILM-COATED TABLETS

PACKAGE LEAFLET: INFORMATION FOR THE USER

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. What Atorvastatin Film-Coated Tablets are and what they are used for
2. Before you take Atorvastatin Film-Coated Tablets
3. How to take Atorvastatin Film-Coated Tablets
4. Possible side effects
5. How to store Atorvastatin Film-Coated Tablets
6. Further information

1 WHAT ATORVASTATIN FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Atorvastatin belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

Atorvastatin is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and lifestyle changes on their own have failed. If you are at an increased risk of heart disease, Atorvastatin can also be used to reduce such risk even if your cholesterol levels are normal. A standard cholesterol lowering diet should be continued during treatment. Cholesterol is a naturally occurring substance in the body necessary for normal growth. However, if there is too much cholesterol in your blood it can be deposited on the walls of the blood vessels, which may eventually become blocked. This is one of the most common causes of heart disease. It is accepted that raised cholesterol levels increase the risk of heart disease. Other factors that will increase the risk of heart disease include high blood pressure, diabetes, increased weight, lack of exercise, smoking, or a family history of heart disease.

2 BEFORE YOU TAKE ATORVASTATIN FILM-COATED TABLETS

Do not take Atorvastatin Film-Coated Tablets

- If you are hypersensitive (allergic) to atorvastatin or to any similar medicines used to lower blood lipids or to any of the other ingredients of the medicine – see section 6 for details
- If you have or have ever had a disease that affects the liver
- If you have had any unexplained abnormal blood tests for liver function
- If you are a woman able to have children and not using reliable contraception
- If you are pregnant, trying to become pregnant or breast-feeding
- If you have a muscle disorder called myopathy (repeated or unexplained muscle pains or weakness).

Take special care with Atorvastatin Film-Coated Tablets

The following are reasons why Atorvastatin Film-Coated Tablets may not be suitable for you:

- If you have kidney problems
- If you have an under-active thyroid gland (hypothyroidism)
- If you have had repeated or unexplained muscle aches or pains, a personal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other ‘-statin’ or ‘-fibrate’ medicines)
- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years.

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your Atorvastatin treatment to predict your risk of muscle-related side effects. The risk of muscle-related side effects is known to increase if certain medicines are taken at the same time as atorvastatin (see ‘Taking other medicines’ below).

Check with your doctor or pharmacist before taking Atorvastatin Film-Coated Tablets if you have severe respiratory failure.

The effectiveness and safety of Atorvastatin Film-Coated Tablets has not been studied for longer than a year in children and teenagers under 18 years of age. Its effects have not been investigated in children under 10 years of age or in girls who have not started having periods.

Taking other medicines

There are some medicines that may change the effect of Atorvastatin, or their effect may be changed by Atorvastatin. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side effects, including the important but rare muscle-wasting condition known as rhabdomyolysis (see section 4 below):

- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole, rifampicin
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid, derivatives, colestipol, ezetimibe
- Some calcium channel blockers used for angina or high blood pressure, e.g. nifedipine, diltiazem; medicines to regulate your heart rhythm e.g. digoxin
- Some benzodiazepines used for anxiety and other conditions, e.g. nefazodone
- Protease inhibitors used in the treatment of HIV, e.g. nelfinavir
- Other medicines known to interact with atorvastatin include: warfarin (which reduces blood clotting); oral contraceptives; phenytoin, carbamazepine or phenobarbital (which are anticonvulsants for epilepsy); antacids (indigestion products containing aluminium or magnesium) and St. John’s wort (which is a herbal remedy).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription.

Taking Atorvastatin Film-Coated Tablets with food and drink

See section 3 for instructions on how to take Atorvastatin Film-Coated Tablets. You should take the following information into account:

Grapefruit juice

Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of atorvastatin.

Alcohol

Avoid drinking too much alcohol while taking this medicine. See section 2 ‘Take special care with Atorvastatin Film-Coated Tablets’ for details.

Pregnancy and breast-feeding

Do not take Atorvastatin Film-Coated Tablets if you are pregnant or if you are trying to become pregnant. Women of child-bearing age must take appropriate contraceptive measures.

Do not take Atorvastatin Film-Coated Tablets if you are breast-feeding.

The safety of atorvastatin during pregnancy and breast-feeding has not been established.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive if this medicine affects your ability to drive. Do not use any tools or machines if your ability to use them is affected by this medicine.

3 HOW TO TAKE ATORVASTATIN FILM-COATED TABLETS

The usual starting dose of Atorvastatin Film-Coated Tablets is 10 mg once a day. This may be increased if necessary by your doctor until you are taking the amount you need. Your doctor will adapt the dosage at intervals of 4 weeks or more. The maximum dose of Atorvastatin Film-Coated Tablets is 80 mg once daily.

Children and adolescents from 4 to 17 years of age:

The usual starting dose of Atorvastatin Film-Coated Tablets is 10 mg once a day. Since the experience in children and adolescents is limited, the use of Atorvastatin Film-Coated Tablets in this age group will be supervised by a specialist.

Atorvastatin Film-Coated Tablets should be swallowed whole with a drink of water, and can be taken at any time of day, with or without food. However, try to take your tablet at the same time every day.

Always take Atorvastatin Film-Coated Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with Atorvastatin Film-Coated Tablets.

The duration of treatment with Atorvastatin Film-Coated Tablets is determined by your doctor.

Please ask your doctor if you think that the effect of Atorvastatin Film-Coated Tablets is too strong or too weak.

If you take more Atorvastatin Film-Coated Tablets than you should

If you accidentally take too many Atorvastatin Film-Coated Tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take Atorvastatin Film-Coated Tablets

If you forget to take a dose, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Atorvastatin Film-Coated Tablets If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Atorvastatin Film-Coated Tablets can cause side effects, although not everybody gets them. The following side effects have been reported. They are listed according to frequency as follows:

Common:	affects 1 to 10 users in 100
Uncommon:	affects 1 to 10 users in 1,000
Rare:	affects 1 to 10 users in 10,000
Very rare:	affects less than 1 user in 10,000

The following side effects are important and will require immediate action if you experience them. You should stop taking Atorvastatin Film-Coated Tablets and see your doctor immediately if the following symptoms occur:

Very rare side effects:

- Sudden allergic reaction with shortness of breath, wheezing, rash and a drop in blood pressure
- Swelling of the face, tongue and windpipe which can cause great difficulty in breathing
- Serious blistering condition of the skin, mouth, eyes and genitals

Rare side effects:

- Muscle wasting or inflammation which can progress to become a serious, potentially life-threatening condition called 'rhabdomyolysis'. It can occur for no apparent reason (e.g. not related to muscle exercise). If you have muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature, stop taking Atorvastatin Film-Coated Tablets and tell your doctor immediately.

The following side-effects have also been reported:

Common side effects:

- Nausea, abdominal pain, constipation, wind, indigestion, headache, muscle pain, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions, numbness or tingling in fingers and toes, reduced skin sensation, joint pain, back pain, swelling, especially of the ankles (oedema), tiredness, skin rash, itching.

Uncommon side effects:

- Loss of appetite, vomiting, hives, sore and weak muscles, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, feeling unwell, impotence, hair loss, inflammation of the pancreas leading to stomach pain (pancreatitis), raised or lowered blood sugar levels (if you have diabetes, you should monitor your blood sugar levels closely).

Rare side effects:

- Liver inflammation (hepatitis), jaundice (yellowing of the skin and whites of the eyes), patchy red rash (erythema multiforme), muscle cramps.

Very rare side effects:

- Altered taste, visual disturbance, hearing loss, breast enlargement in men (gynaecomastia), tendon injury, severe liver problems.

Changes in blood test results that report on how your liver is working (frequency not given).

The following adverse events have been reported with some statins (frequency not given): sleep disturbances including nightmares, memory loss, sexual difficulties, depression and breathing problems including persistent cough and/or shortness of breath or fever.

If you experience side effects, please inform your doctor. He/she will decide on the further steps needed.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE ATORVASTATIN FILM-COATED TABLETS

Keep out of the reach and sight of children.

Do not use Atorvastatin Film-Coated Tablets after the expiry date which is stated on the blister and outer packaging after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What Atorvastatin Film-Coated Tablets contain

- The active substance is atorvastatin
 - Each 10 mg tablet contains 10 mg of atorvastatin as atorvastatin calcium
 - Each 20 mg tablet contains 20 mg of atorvastatin as atorvastatin calcium
 - Each 40 mg tablet contains 40 mg of atorvastatin as atorvastatin calcium
 - Each 80 mg tablet contains 80 mg of atorvastatin as atorvastatin calcium
- The other ingredients in the tablet core are microcrystalline cellulose, sodium carbonate anhydrous, maltose, croscarmellose sodium and magnesium stearate. The other ingredients in the film-coating are hypromellose (E464), hydroxypropylcellulose, triethyl citrate (E1505), polysorbate 80 and titanium dioxide (E171).

What Atorvastatin Film-Coated Tablets look like and the contents of the pack

- 10 mg: Atorvastatin Film-Coated Tablets are white to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 9.7 mm x 5.2 mm.
- 20 mg: Atorvastatin Film-Coated Tablets are white to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 12.5 mm x 6.6 mm.
- 40 mg: Atorvastatin Film-Coated Tablets are white to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 15.6 mm x 8.3 mm.
- 80 mg: Atorvastatin Film-Coated Tablets are white to off-white, elliptic, biconvex and smooth film-coated tablets. The dimensions of each tablet are approximately 18.8 mm x 10.3 mm.
- Atorvastatin Film-Coated Tablets are available in aluminium-aluminium blisters containing 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
TEVA UK Limited, Eastbourne, BN22 9AG

Manufacturer
BELMAC, S.A., 50016 Zaragoza, SPAIN.

This leaflet was last revised in June 2010.

PL 00289/1289 - 1292

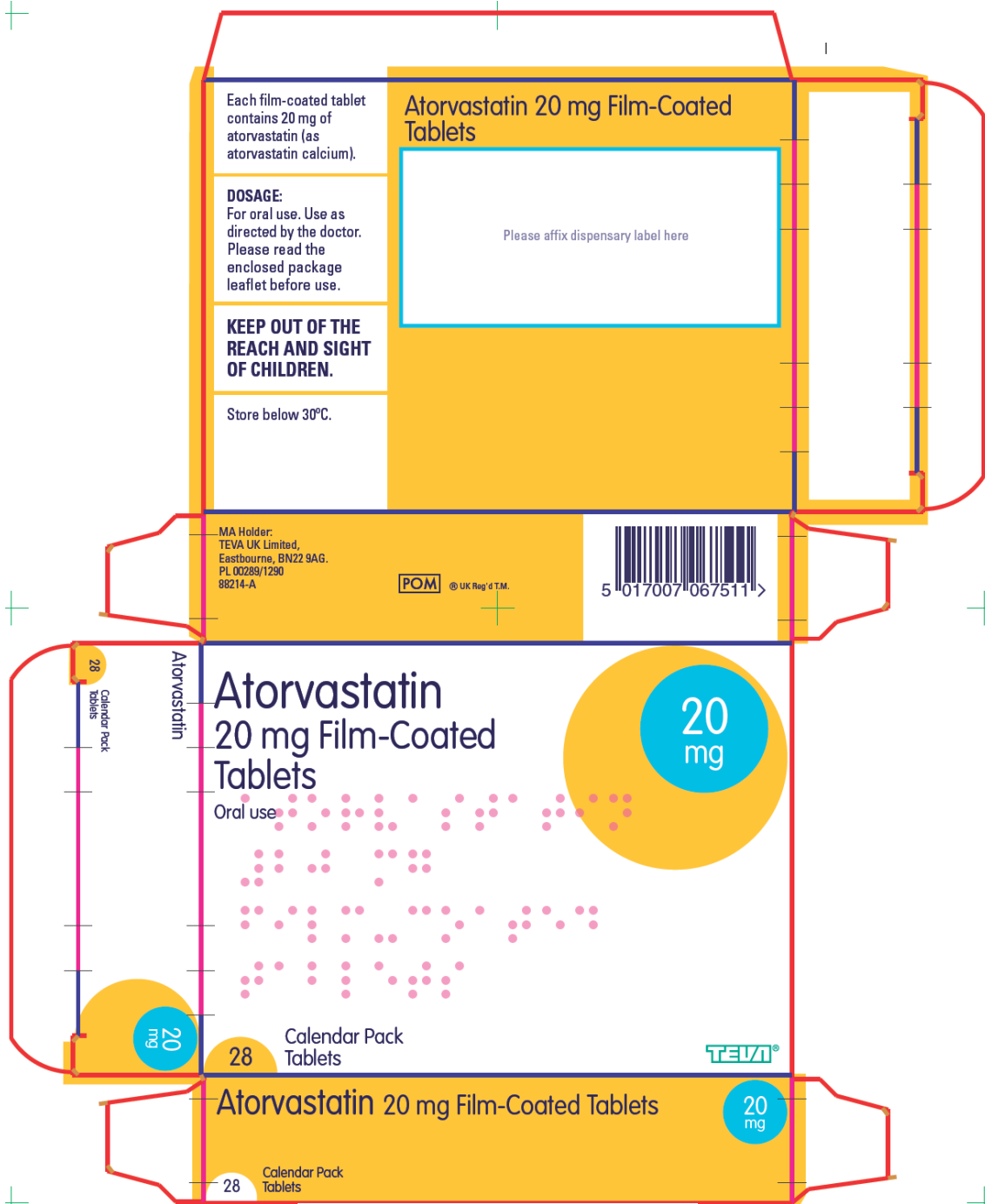


88245-A

Module 4 Labelling

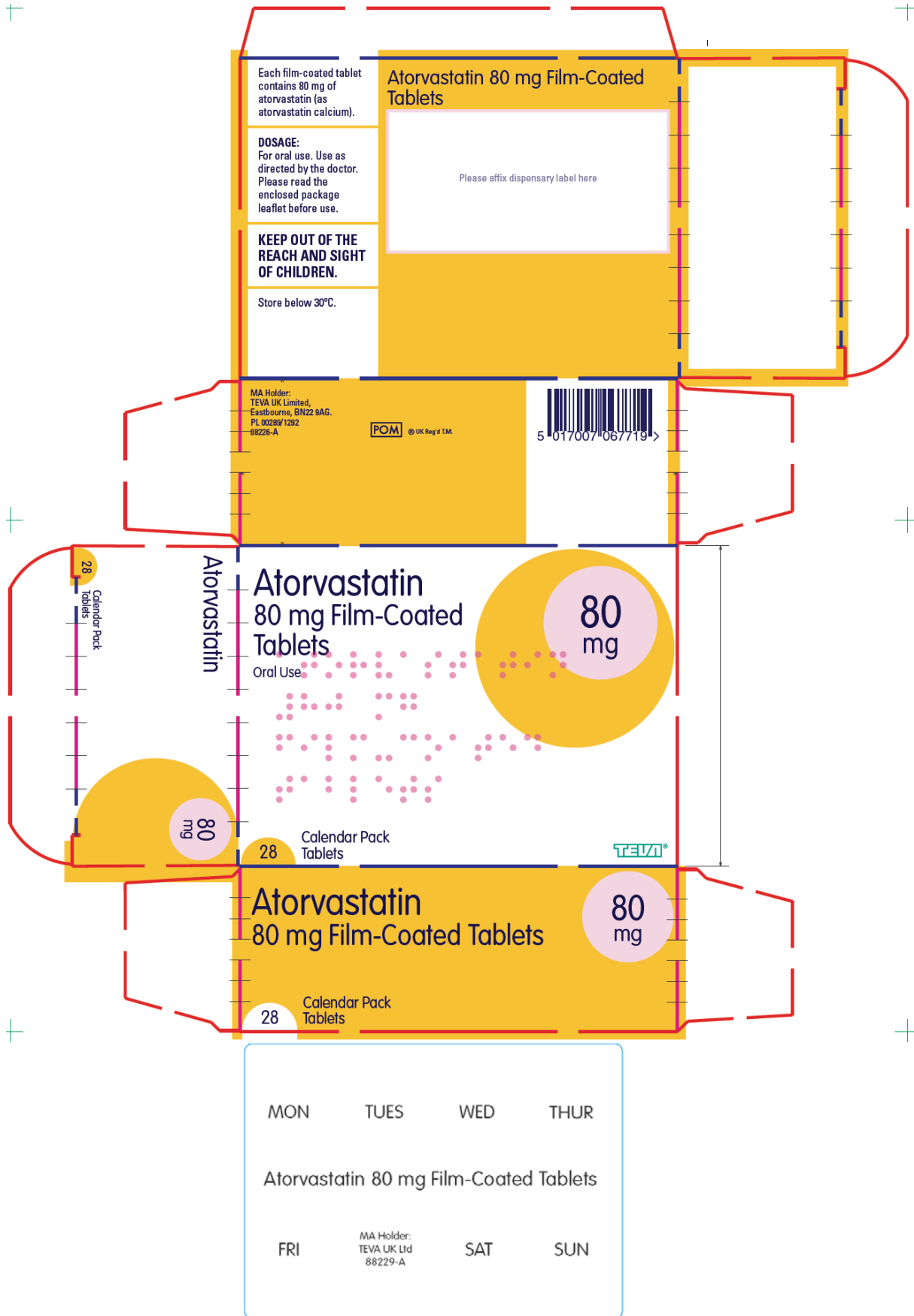


MON	TUES	WED
Atorvastatin 10 mg Film-Coated Tablets		
THUR		
MA Holder: TEVA UK Ltd		88211-A
FRI	SAT	SUN



MON	TUES	WED
Atorvastatin 20 mg Film-Coated Tablets		
THUR		
MA Holder: TEVA UK Ltd		88217-A
FRI	SAT	SUN





Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Atorvastatin 10mg, 20mg, 40mg and 80mg Film-Coated Tablets (PL 00289/1289-92; UK/H/2900/001-4/DC) could be approved. These applications were submitted by the decentralised procedure, with the UK as reference member state (RMS), and Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia as concerned member states (CMS).

The products are prescription-only medicines for the treatment of:

- **Hypercholesterolaemia:**
Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients 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 non pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total-C and LDL-C in patients 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 patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors.

These are applications made under the decentralised procedure (DCP), according to Article 10.1 of 2001/83/EC, as amended, for generic medicinal products of Lipitor 10mg, 20mg, 40mg and 80mg Tablets, which were originally granted licences in 1997 to Pfizer Ireland Pharmaceuticals Limited, UK.

Atorvastatin is a 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitor that reduces blood lipid concentrations. It is taken orally and is used in the treatment of hyperlipidaemias.

No new non-clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of originator products that have been licensed for over 10 years.

No new clinical studies were conducted, which is acceptable given that the applications are for generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 05 July 2010. After a subsequent national phase, the licences were granted in the UK on 03 August 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Atorvastatin 10, 20, 40 and 80mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Atorvastatin
Pharmacotherapeutic classification (ATC code)	HMG-CoA reductase inhibitors (C10AA05)
Pharmaceutical form and strength(s)	10, 20, 40 and 80mg film-coated tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/2900/001-4/DC
Reference Member State	United Kingdom
Member States concerned	UK/H/2900/001-4/DC: Austria, Belgium, Bulgaria, Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Ireland, Italy, Lithuania, Luxembourg, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia
Marketing Authorisation Number(s)	PL 00289/1289-92
Name and address of the authorisation holder	TEVA UK Ltd, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

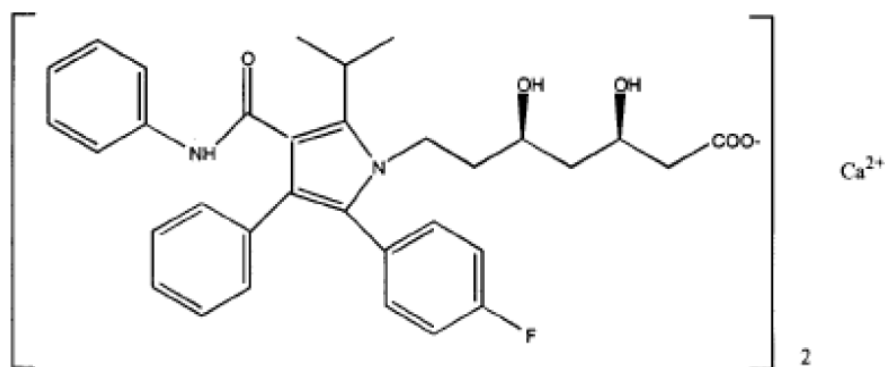
III.1 QUALITY ASPECTS

S. Active substance

INN: Atorvastatin calcium

Chemical name: [R-(R*, R*)]-2-(4-Fluorophenyl)-β,δ,-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt(2:1)

Structure:



Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}$

Molecular Weight: 1155.36

Appearance: White to off white coloured powder.

Atorvastatin calcium was not the subject of a European Pharmacopoeia monograph at the time of assessment.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients microcrystalline cellulose, sodium carbonate anhydrous, maltose, croscarmellose sodium, magnesium stearate, hypromellose (E464), hydroxypropylcellulose, triethyl citrate (E1505), polysorbate 80 and titanium dioxide (E171).

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of maltose and hypromellose (E464) which comply with suitable National Formulary specifications. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients are of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent tablet dosage form of Atorvastatin Film-Coated Tablets, comparable to the innovator product Zarator (Pfizer, Spain) which is the same as Lipitor Tablets (Pfizer Ireland Pharmaceuticals Limited) the reference product in the UK.

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of all strengths of product, along with an appropriate account of the manufacturing process.

Finished Product Specification

The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

Aluminium-aluminium blisters in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 tablets.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of all strengths of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions "Store below 30°C".

Bioequivalence/bioavailability

Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a risk management plan for these products.

MAA forms

The MAA forms are pharmaceutically satisfactory.

Expert report

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion

The grant of marketing authorisations is recommended.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well-known, no further non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose crossover study to compare the pharmacokinetics of the test product Atorvastatin 80mg Tablets versus the reference product Zarator 80mg Tablets (Pfizer, Spain) in healthy adult volunteers under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The two treatment arms were separated by at least a 7-day washout period.

Table 1: The pharmacokinetic results for atorvastatin (presented as log transformed test/reference ratios and 90% confidence intervals) are presented below:

Treatment	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)
Test	161.08	166.47	40.70
Reference	155.00	162.85	39.69
Ratio (90% CI)	1.04 (0.96-1.14)	1.02 (0.93-1.11)	1.01 (0.89-1.15)

Table 2: The pharmacokinetic results for the metabolite ortho-hydroxy-atorvastatin (presented as log transformed test/reference ratios and 90% confidence intervals) are presented below:

Treatment	AUC _{0-t} (ng.h/ml)	AUC _{0-∞} (ng.h/ml)	C _{max} (ng/ml)
Test	235.56	241.86	35.88
Reference	241.57	248.26	37.75
Ratio (90% CI)	0.98 (0.90-1.08)	0.98 (0.90-1.07)	0.97 (0.83-1.14)

Bioequivalence was demonstrated for the parent compound (atorvastatin) and the active metabolite (ortho-hydroxy-atorvastatin). Therefore, the proposed product is equivalent to the reference product.

As the 10, 20, 40, and 80mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the extrapolation of results and conclusions from the bioequivalence study on the 80mg strength to the 10 and 20mg and 40mg strengths is justified.

Efficacy

No new data on the efficacy have been submitted and none are required for these types of applications.

Safety

No new or unexpected safety issues were raised by the bioequivalence data.

SPC, PIL, Labels

The SPC, PIL and labels are medically acceptable. The SPCs are consistent with those for the originator products.

Clinical Expert Report

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion

The grant of marketing authorisations is recommended.

**IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY**

The important quality characteristics of Atorvastatin 10, 20, 40 and 80mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the risk-benefit balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's 80mg Tablets and its respective reference product. As the 10, 20 and 40mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 80mg strength can be extrapolated to the 10, 20 and 40mg strength tablets.

No new or unexpected safety concerns arise from these applications.

The SPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with atorvastatin is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome