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

(atorvastatin calcium)

UK/H/2381/01-04/DC
UK licence numbers: PL 18179/0001-4

Midas Pharma GmbH
LAY SUMMARY

On 9th September 2010, the MHRA granted Midas Pharma Marketing Authorisations (licences) for the medicinal products Atorvastatin 10mg, 20mg, 40mg and 80mg Tablets. These medicines are available on prescription from your doctor.

It is accepted that raised blood cholesterol levels increase the risk of heart disease. Other factors that will increase the risk of heart disease included high blood pressure, diabetes, increased weight, lack of exercise, smoking, or a family history of heart disease.

Atorvastatin Tablets belong to a group of medicines known as statins. Statins are used to:

- lower blood fats known as cholesterol and triglycerides when a low fat diet and lifestyle changes on their own have not been enough to do so
- reduce the risk of heart disease in patients at high risk, even if your cholesterol levels are normal.

It is important to continue with your cholesterol lowering diet and lifestyle changes during treatment with Atorvastatin.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of Atorvastatin 10mg, 20mg, 40mg and 80mg Tablets outweigh the risks; hence Marketing Authorisations have been granted.
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## Module 1

### Information about Initial Procedure

| Product Name | Atorvastatin 10mg film-coated Tablets  
|              | Atorvastatin 20mg film-coated Tablets  
|              | Atorvastatin 40mg film-coated Tablets  
|              | Atorvastatin 80mg film-coated Tablets  |
| Type of Application | Generic, Article 10.1 |
| Active Substance | Atorvastatin calcium |
| Form | Film-coated tablets |
| Strength | 10mg, 20mg, 40mg, and 80mg |
| MA Holder | Midas Pharma GmbH  
|           | Rheinstrasse 49  
|           | Ingelheim  
|           | D-55218  
|           | Germany |
| Reference Member State (RMS) | UK |
| Concerned Member State / s (CMS) | Germany |
| Procedure Number | UK/H/2381/01-04/DC |
| Timetable | Day 210 – 11\textsuperscript{th} August 2010 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPC) for Atorvastatin 10mg, 20mg, 40mg, and 80mg film-coated tablets (PL 18179/0001-4) is as follows – Differences are highlighted:

1 NAME OF THE MEDICINAL PRODUCT

- Atorvastatin 10 mg film-coated Tablets
- Atorvastatin 20 mg film-coated Tablets
- Atorvastatin 40 mg film-coated Tablets
- Atorvastatin 80 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10/20/40/80 mg tablet contains 10/20/40/80 mg atorvastatin as atorvastatin calcium.

Excipients:
- Each Atorvastatin 10mg film-coated tablet contains 65mg lactose and 3.9mg sucrose
- Each Atorvastatin 20mg film-coated tablet contains 129mg lactose and 7.8mg sucrose
- Each Atorvastatin 40mg film-coated tablet contains 258mg lactose and 15.5mg sucrose
- Each Atorvastatin 80mg film-coated tablet contains 516mg lactose and 31.1mg sucrose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet:
- Atorvastatin 10mg tablets: White, oblong (capsule shaped) film coated tablets debossed 'RDY' on one side and '571' on the other side.
- Atorvastatin 20mg tablets: White, oblong (capsule shaped) film coated tablets debossed 'RDY' on one side and '570' on the other side.
- Atorvastatin 40mg tablets: White, oblong (capsule shaped) film coated tablets debossed 'R569' on one side and plain on the other side.
- Atorvastatin 80mg tablets: White, oblong (oval shaped) film coated tablets debossed 'R568' on one side and plain on the other side.

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 nonpharmacological 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 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

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 in adults 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.

For oral administration.
Current consensus guidelines should be consulted to establish treatment goals for individual patients.

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

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

Heterozygous Familial Hypercholesterolaemia

Patients should be started with 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 (e.g., colestipol) may be combined with 40 mg atorvastatin.

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 hypercholesterolemia 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 either plasma concentrations or lipid effects of atorvastatin; thus, no
adjustment of dose is required.

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

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

Paediatric use
Experience in paediatric population is limited to a small number of patients with severe dyslipidemia,
such as homozygous familial hypercholesterolemia (see section 5.1). Developmental safety data in this
population have not been evaluated.
Use in paediatric patients should only be carried out by specialists.
The recommended starting dose in this population is 10 mg of atorvastatin per day.
However, doses above 20mg/day have not been investigated in patients aged <18 years.
4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients of this medication
- Active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- Myopathy
- Pregnancy
- Breast-feeding
- Women of child-bearing potential not using appropriate contraceptive measures.

4.4 Special warnings and precautions for use

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

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 CHD who had a recent stroke or TIA there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Section 5.1).

Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated CPK levels (> 10 times ULN), myoglobinemia and myoglobinuria which may lead to renal failure. Myopathy must be considered in any patient under statin therapy presenting with unexplained muscle symptoms such as pain or tenderness, muscle weakness or muscle cramps. In such cases serum creatine phosphokinase (CPK) levels should be measured.

Before treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis.

A creatine phosphokinase (CPK) level should be measured before starting statin treatment in the following situations:

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

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

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

Creatine phosphokinase measurement
Creatine phosphokinase (CPK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CPK increase as this makes value interpretation difficult. If CPK levels are significantly elevated at baseline (>5 times ULN), levels should be 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.

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicaments such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibric acid derivates or HIV-protease inhibitors (see section 4.5 and section 4.8).

The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, a lower starting dose of atorvastatin is recommended. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (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.

Paediatric use

In patients younger than 18 years of age, efficacy and safety have not been studied for treatment periods more than 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.

This product contains lactose: Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

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. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see section 4.4).

When patients are receiving drugs that increase the plasma concentration of atorvastatin, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used. (see Section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized 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 medicinal agents (see section 4.4).

**Inhibitors of P-glycoprotein**
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 and P-glycoprotein transporters. Inhibitors of these transporters (e.g. ciclosporin) can increase the systemic exposure of atorvastatin. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an 8.7 fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with ciclosporin is necessary, the atorvastatin dose should not exceed 10 mg.

**Erythromycin, clarithromycin**
Erythromycin and clarithromycin are known inhibitors of cytochrome P450 3A4. Co-administration of atorvastatin 80 mg OD and erythromycin (500 mg QID) resulted in a 33 % increase in exposure to total atorvastatin activity. Co-administration of atorvastatin 10 mg OD and clarithromycin (500 mg bid) resulted in a 4.4 fold increase in exposure to atorvastatin. In cases where co-administration of clarithromycin with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At doses exceeding 40 mg, appropriate clinical monitoring of these patients is recommended.

**Azithromycin**
Co-administration of atorvastatin (10 mg once daily) and azithromycin (500 mg once daily) did not alter the plasma concentrations of atorvastatin.

**Itraconazole**
Concomitant administration of atorvastatin 20-40 mg and itraconazole 200 mg daily resulted in a 2.5-3.3-fold increase in atorvastatin AUC. In cases where co-administration of itraconazole with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 40 mg daily. Patients who normally require 80 mg of atorvastatin should either reduce their dosage during concomitant itraconazole treatment, or alternatively (for short courses of this antifungal medicine) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

**Protease inhibitors**
Co-administration of atorvastatin and protease inhibitors, known inhibitors of cytochrome P450 3A4, was associated with increased plasma concentrations of atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

**Diltiazem hydrochloride**
Co-administration of atorvastatin 40 mg with diltiazem 240 mg resulted in a 51% increase in atorvastatin AUC. After initiation of diltiazem or following dosage adjustment, lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

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

**Grapefruit juice**
Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37% and a decreased AUC of 20.4% for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (Atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. 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 (e.g. efavirenz, rifampicin, St.John’s wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampicin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampicin is recommended, as delayed administration of atorvastatin after administration of rifampicin has been associated with a significant reduction in atorvastatin plasma concentrations.
Verapamil and Amiodarone
Interaction studies with Atorvastatin and verapamil or amiodarone have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

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 fibric acid derivatives. Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in exposure to atorvastatin.

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 approx. 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 approx. 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.

Phenzone
Co-administration of multiple doses of atorvastatin and phenzone showed little or no detectable effect in the clearance of phenzone.

Cimetidine
An interaction study with cimetidine and atorvastatin was conducted, and no interaction was seen.

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

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 (see section 4.3).

The safety of atorvastatin in pregnancy and lactation has not been established.
There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or fetuses. 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 atorvastatin or its metabolites are excreted in human milk.

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

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 side effects attributed to atorvastatin.

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

Estimated frequencies of events are ranked according to the following convention: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (≤ 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.

Endocrine disorders
Uncommon: hyperglycaemia, hypoglycaemia.

Psychiatric disorders
Common: insomnia.
Uncommon: amnesia.

Nervous system disorders
Common: headache, dizziness, paraesthesia, hypoaesthesia.
Uncommon: peripheral neuropathy.
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

Hepato-biliary disorders
Rare: hepatitis, cholestatic jaundice.
Very rare: hepatic failure.
Skin and subcutaneous tissue disorders

Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Musculoskeletal and connective tissue disorders
Common: myalgia, arthralgia.
Uncommon: myopathy, muscle cramps
Rare: myositis, rhabdomyolysis.
Very rare: tendon rupture.

Reproductive system and breast disorders
Uncommon: impotence.
Very rare: gynecomastia.

General disorders and administration site conditions
Common: asthenia, chest pain, back pain, peripheral oedema, fatigue.
Uncommon: malaise, weight gain.

Investigations
As with other HMG-CoA reductase inhibitors elevated serum transaminases have been reported in patients receiving Atorvastatin. These changes were usually mild, transient, and did not require interruption of treatment. Clinically important (> 3 times upper normal limit) elevations in serum transaminases occurred in 0.8% patients on Atorvastatin. These elevations were dose related and were reversible in all patients.

Elevated serum creatine phosphokinase (CPK) levels greater than 3 times upper limit of normal occurred in 2.5% of patients on Atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Atorvastatin-treated patients (see section 4.4).

Class attribution effects (frequencies not stated):
The following adverse events have been reported with some statins:
- Sleep disturbances, including insomnia and nightmares
- Memory loss
- Sexual dysfunction
- Depression
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4)

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Lipid modifying agents, HMG CoA reductase inhibitors
ATC code: C10AA05

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into 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 high affinity LDL receptor.
Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and 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 medication.

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.

### Dose Response in Patients with Primary Hypercholesterolaemia

<table>
<thead>
<tr>
<th>Atorvastatin Dose (mg)</th>
<th>N</th>
<th>Total-C (%)</th>
<th>LDL-C (%)</th>
<th>Apo B (%)</th>
<th>TG (%)</th>
<th>HDL-C (%)</th>
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</table>

Adjusted Mean % Change from Baseline

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

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

**Atherosclerosis**

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

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

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

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

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

**Prevention of cardiovascular disease**

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

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

The absolute and relative risk reduction effect of atorvastatin is as follows (Table 1):

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction1 (%)</th>
<th>No of events (Atorvastatin vs. placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal CHD plus non-fatal MI</td>
<td>36%</td>
<td>1.1%</td>
<td>100 vs. 154</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total cardiovascular events and revascularization procedures</td>
<td>20%</td>
<td>1.9%</td>
<td>389 vs. 483</td>
<td>0.0008</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>29%</td>
<td>1.4%</td>
<td>178 vs. 247</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

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

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

The absolute and relative risk reduction effect of Atorvastatin was as follows (Table 2):

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction1 (%)</th>
<th>No of events (Atorvastatin vs. placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)</td>
<td>37%</td>
<td>3.2%</td>
<td>83 vs. 127</td>
<td>0.0010</td>
</tr>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>1.9%</td>
<td>38 vs. 64</td>
<td>0.007</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>1.3%</td>
<td>21 vs. 39</td>
<td>0.0163</td>
</tr>
</tbody>
</table>

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 4731 patients who had a stroke or transient ischaemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dl (3.4 mmol/l). The mean LDL-C was 73 mg/dl (1.9 mmol/l) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

In a post-hoc analysis, atorvastatin 80 mg reduced the incidence of ischemic stroke (218/2365, 9.2% vs. 274/2366, 11.6%, p=0.01) and increased the incidence of haemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

- The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk of ischemic 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 ischemic stroke was also decreased in these patients (79/708 for atorvastatin versus 102/701 for placebo; HR 0.76; 95% CI, 0.57-1.02). It is possible that the net risk of stroke is increased in patients with prior lacunar infarct who receive atorvastatin 80 mg/day.

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

Heterozygous Familial Hypercholesterolaemia in Paediatric Patients
In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolaemia (FH) or severe hypercholesterolaemia were randomised to atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. Inclusion in the study required 1) a baseline LDL-C level ≥4.91 mmol/l or 2) a baseline LDL-C ≥4.14 mmol/l and positive family history of FH or documented premature cardiovascular disease in a first- or second degree relative. The mean baseline LDL-C value was 5.65 mmol/l (range: 3.58-9.96 mmol/l) in the atorvastatin group compared to 5.95 mmol/l (range: 4.14-8.39 mmol/l) in placebo group. The dosage if atorvastatin (once daily) was 10mg for the first 4 weeks and up-titrated to 20mg if the LDL-C level was>3.36 mmol/l. The number of atorvastatin-treated patients who required up-titration to 20mg after week 4 during the double-blind phase was 80 (57.1%).

Atorvastatin significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipoprotein B during the 26-week double-blind phase (see Table 3).

<table>
<thead>
<tr>
<th>DOSAGE</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>47</td>
<td>-1.5</td>
<td>-0.4</td>
<td>1.9</td>
<td>1.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>140</td>
<td>-31.4</td>
<td>-39.6</td>
<td>2.8</td>
<td>-12.0</td>
<td>-34.0</td>
</tr>
</tbody>
</table>

The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the Atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26-week double-blind phase.
In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual length in girls. Atorvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. The safety and efficacy of doses above 20mg have not been studied in controlled trials in children. The long-term efficacy of atorvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

5.2 Pharmacokinetic properties

Pharmacokinetics and Drug Metabolism

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (Cmax) 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 ≥ 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
- Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: Pharmacokinetic data in the paediatric population are not available.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for Cmax and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal 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 (approx. 16-fold in Cmax and approx. 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**
Butyl hydroxyanisole
Cellulose, microcrystalline
Silica, colloidal anhydrous
Lactose monohydrate
Sodium laurilsulfate
Sodium hydrogen carbonate
Crospovidone (Type A)
Magnesium stearate
Dimethicone 400
Sucrose
Sorbitan tristearate
Macrogol 40 stearate,
2-bromo-2-nitropropane-1,3-diol

**Film coating**
Opadry OYL-28900 White – contains lactose monohydrate, hydroxypropyl methylcellulose (hypromellose 15 CP), titanium dioxide (E171) and macrogol/PEG 4000.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C

6.5 Nature and contents of container
PVC /Aluminium/ Polyamide /Aluminium blisters.

- **Carton pack sizes**: 10, 14, 28, 30, 50, 56 and 100 - 10mg
- **Carton pack sizes**: 10, 28, 30, 50 and 100 - 20mg
- **Carton pack sizes**: 28, 30, 50 and 100 - 40mg
- **Carton pack sizes**: 28, 30, 50 and 100 - 80mg

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Any unused product or waste material should be disposed off in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER
MIDAS PHARMA GMBH
RHEINSTRASSE 49
INGELHEIM
D-55218
GERMANY
| 8 | MARKETING AUTHORISATION NUMBER(S) |
|   | PL 18179/0001  |
|   | PL 18179/0002  |
|   | PL 18179/0003  |
|   | PL 18179/0004  |

| 9 | DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION |
|   | 09/09/2010       |

| 10 | DATE OF REVISION OF THE TEXT |
|    | 09/09/2010       |
Module 3

Product Information Leaflet text

Atorvastatin 10, 20, 40, 80 mg film-coated Tablets:

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 get 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

It is accepted that raised blood 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.

Atorvastatin tablets belong to a group of medicines known as statins. Statins are used to:
- lower blood fats known as cholesterol and triglycerides when a low fat diet and lifestyle changes on their own have not been enough to do so.
- reduce the risk of heart disease in patients at high risk, even if your cholesterol levels are normal.

It is important to continue with your cholesterol lowering diet and lifestyle changes during treatment with Atorvastatin.

2. Before you take Atorvastatin Film-coated tablets

Do not take Atorvastatin film-coated Tablets if you:
- are allergic (hypersensitive) to atorvastatin, to similar medicines used to lower lipids or to any of the other ingredients in the tablets (Section 6)
- have or have ever had a disease which affects the liver
- have had any unexplained abnormal blood tests for liver function
- have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains),
- are a woman able to become pregnant and not using reliable contraception
- are pregnant, trying to become pregnant or breast-feeding.
- drink excessive amounts of alcohol

Take special care with Atorvastatin film-coated Tablets if you:
- have kidney problems
- have an under-active thyroid gland (hypothyroidism)
- have had repeated or unexplained muscle aches, pains or other muscle problems or there is a family history of muscle problems.
- are older than 70 years
- have had muscular problems during previous treatment with other lipid-lowering medicines (e.g. other statins or fibrates)
- regularly drink a large amount of alcohol

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your treatment to assess your risk of muscle-related side effects.

Check with your doctor or pharmacist before taking Atorvastatin film-coated Tablets if you have severe respiratory failure

Taking other medicine:
Some medicines may interact with atorvastatin. This could make one or both of the medicines less effective or increase the risk of side-effects, including the important but rare muscle wasting condition known as rhabdomyolysis (see below).
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:

- medicines used to alter the way your immune system works, e.g. ciclosporin
- certain antibiotics e.g. erythromycin, clarithromycin, rifampicin
- some antifungal medicines e.g. ketoconazole, itraconazole – other medicines to regulate lipid levels, e.g. gemfibrozil, fibrin acid derivatives, colestipol
- some medicines used for angina or high blood pressure e.g. nifedipine
- medicines to regulate your heart rhythm e.g. digoxin
- some medicines used for anxiety and other conditions e.g. diazepam, nefazodone
- medicines used in the treatment of HIV e.g. nevirapine
- warfarin (to reduce blood clotting) – oral contraceptives
- phenytoin (for epilepsy)
- metaclopramide (indigestion products)
- St. John’s wort

Taking Atorvastatin film-coated Tablets with food and drink:

Whilst taking Atorvastatin do not drink more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of the tablets.

Avoid drinking too much alcohol while taking this medicine.

Pregnancy and breast-feeding

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

Do not take Atorvastatin tablets if you are pregnant or trying to become pregnant or are breast-feeding. If you are a woman of child-bearing potential you have to use appropriate contraceptive measures. If you are trying to become pregnant, your doctor will advise you to stop taking atorvastatin about one month before you plan to conceive.

Driving and using machines:

Atorvastatin tablets may affect your ability to drive or operate machinery.

Important information about some of the ingredients of Atorvastatin film-coated Tablets:

This Product contains sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Atorvastatin Film-coated Tablets:

Low cholesterol diet

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should follow while taking Atorvastatin tablets.

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

Swallow the tablets whole with a drink of water. They can be taken at any time of day, with or without food. However, try to take your tablet at the same time every day.

The usual starting dose is 10 mg once a day.

Children up to 18 yrs old should be treated by a specialist.

If needed, your doctor may increase this until you are taking the amount you need. Your doctor may change the dosage at intervals of 4 weeks or more. The maximum dose is 80 mg once daily.

If you take more Atorvastatin film-coated Tablets than you should:

If you accidentally take too many Atorvastatin tablets (more than your usual daily dose), tell your doctor at once.

If you forget to take Atorvastatin film-coated Tablets:

If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.
If you stop taking Atorvastatin film-coated Tablets:

You should take Atorvastatin tablets regularly to get the maximum benefit, even if you are feeling better or well.

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 tablets can cause side effects, although not everybody gets them. Side effects may occur with the following frequencies:

The following side effects are important and will require immediate action if you experience them. Stop taking the tablets and contact a doctor at once if you experience any of the following serious side effects:

Rare (affects 1 to 10 users in 10,000)

- muscle wasting or inflammation which has very rarely progressed to become a serious potentially life-threatening condition (called "rhabdomyolysis"). These muscle complaints may 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 tablets and tell your doctor immediately.

Very rare (affects less than 1 user in 10,000)

- swelling of the face, tongue and windpipe which can cause great difficulty in breathing
- a sudden severe allergic reaction with shortness of breath, rash, wheezing and drop of blood pressure
- severe, extensive, blistering skin rash

The following side effects have also been reported.

Common (affects 1 to 10 users in 100)

- nausea
- constipation, diarrhea
- indigestion, heartburn
- difficulty sleeping
- dizziness
- skin rash, itching
- pain in the muscles, decreased feeling in the skin
- muscle pain, joint pain, chest pain and back pain.
- inability to retain fluid, swelling caused by fluid retention
- allergy reactions
- feeling weak

Uncommon (affects 1 to 10 users in 1,000)

- loss of appetite
- vomiting
- tinnitus (ringing in the ears and/or head)
- feeling unwell
- weight gain
- loss of memory
- hair loss
- impotence
- pancreatitis (inflammation of the pancreas causing stomach pain),
- unusual or easy bruising and bleeding
- increases and decreases in blood sugar levels. If you have diabetes, you should continue careful monitoring of your blood sugar levels.
- itches

Rare (affects 1 to 10 users in 10,000)

- inflammation of the liver
- jaundice (yellowing of the skin and whites of the eyes).

Very rare (affects less than 1 user in 10,000)

- visual disturbances
- hearing loss
- taste disturbances
- breast enlargement in men.
- tendon injury
- severe liver disease
Other side effects (frequency not given) that have been reported for statins include:
- Sleep disturbances including insomnia and nightmares
- Memory loss
- Sexual difficulties
- Depression
- 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

Store below 25°C. Keep out of the reach and sight of children.
Do not use Atorvastatin tablets after the expiry date which is stated on the blister, carton or label after EXP. The expiry date refers to the last day of that month. Do not use Atorvastatin tablets if you notice visible signs of deterioration such as discolouration or crumbling.

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 contains:
The active substance (the ingredient which makes the tablets work) in your tablets is atorvastatin.
Each film-coated tablet contains 10mg, 20mg, 40mg or 80mg of atorvastatin known as atorvastatin calcium.
The other ingredients are:
Tablet core: Butyl hydroxyanisole, cellulose microcrystalline, silica colloidal anhydrous, lactose monohydrate, sodium laurylsulfate, sodium hydrogen carbonate, crospovidone (Type A), magnesium stearate, dexamethasone 400, sucrose, sorbitan monostearate macrogol 40 stearate, 2-bromo-3-nitropropene 1,3-diol
Tablet coating: Opadry OYL-28000 White — contains lactose monohydrate, hydroxypropyl methylcellulose (hypromellose 15 CP), titanium dioxide (E171) and macrogol PEG 4000

What Atorvastatin film-coated Tablets looks like and contents of the pack:
Atorvastatin tablets are white with a capsule shape.
Atorvastatin 10mg film-coated tablets are marked with RDY on one side and '571' on the other side.
Atorvastatin 20mg film-coated tablets are marked with RDY on one side and '570' on the other side.
Atorvastatin 40mg film-coated tablets are marked with R56 on one side and plain on the other side.
Atorvastatin 80mg film-coated tablets are marked with R56 on one side and plain on the other side.

Atorvastatin film-coated tablets are supplied in blister packs of:
- 10mg: 10, 14, 28, 30, 50, 56 and 100
- 20mg: 10, 28, 30, 50 and 100
- 40mg: 28, 30, 50 and 100
- 80mg: 28, 30, 50 and 100

Marketing authorisation holder and manufacturer:
Midas Pharma GmbH, Rheinstraße 49, 55210 Ingelheim, Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

This leaflet was last updated in (09/2010 date to be inserted).
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PL numbers: 18179/001-004
Module 4

Labelling text

The labelling text is identical for all licences, apart from the strengths, pack sizes and PL numbers. These differences have been highlighted.

1. NAME OF THE MEDICINAL PRODUCT

Atorvastatin 10/20/40/80 mg Film-coated Tablets

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10/20/40/80 mg atorvastatin as atorvastatin calcium.

3. LIST OF EXCIPIENTS

Tablets also contain lactose and sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated Tablet

<table>
<thead>
<tr>
<th>Strength</th>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>10mg</td>
<td>10, 14, 28, 30, 50, 56 and 100</td>
</tr>
<tr>
<td>20mg</td>
<td>10, 28, 30, 50 and 100</td>
</tr>
<tr>
<td>40mg</td>
<td>28, 30, 50 and 100</td>
</tr>
<tr>
<td>80mg</td>
<td>28, 30, 50 and 100</td>
</tr>
</tbody>
</table>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Swallow the tablets whole with a drink of water.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

N/A

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Store below 25°C.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR
WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

No special requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Midas Pharma GmbH, Rheinstrasse 49, 55218 Ingelheim, Germany

12. MARKETING AUTHORISATION NUMBER(S)

PL 18179/0001 / 0002 / 0003 / 0004

13. BATCH NUMBER

Batch No.

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Take as directed by the doctor.

16. INFORMATION IN BRAILLE

Atorvastatin 10 / 20 / 40 / 80 mg Film-coated Tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

(NATURE/TYPE)

1. NAME OF THE MEDICINAL PRODUCT

Atorvastatin 10 / 20 / 40 / 80 mg Film-coated Tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Midas Pharma GmbH, Rheinstrasse 49, 55218 Ingelheim, Germany

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER
Module 5

Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Midas Pharma GmbH Marketing Authorisations for the medicinal products Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets (PL 18179/0001-4, UK/H/2381/01-04/DC) on 9th September 2010. The products are prescription-only medicines (POM).

These are generic applications for Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets, four strengths of atorvastatin, submitted under Article 10.1 of 2001/83 EC, as amended. The applications refer to the UK reference products, Lipitor® 10mg, 20mg, 40mg and 80mg Tablets (PL 16051/0001-3 and 0005 respectively), authorised to Pfizer Ireland Pharmaceuticals on 8th September 1997 (PL 16051/0001-3) and 15th August 2000 (PL 16051/0005). Lipitor® 10mg, 20mg and 40mg Tablets are the innovator products. Lipitor® 10mg, 20mg, 40mg and 80mg Tablets have been authorised in the UK for more than 10 years; thus the period of data exclusivity has expired.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase (ATC code: C10A A05), the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor. Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and 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 10mg, 20mg, 40mg and 80mg film-coated Tablets are indicated for hypercholesterolaemia and for the prevention of cardiovascular disease, as described below:

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 cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1 of SmPC), as an adjunct to correction of other risk factors.
No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Atorvastatin 80mg film-coated Tablets, to that of the reference product, Lipitor® 80mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The products are not of genetic modification and neither have any of their excipients been genetically modified. There are no environmental concerns associated with the method of manufacture or formulation of the products.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Atorvastatin 10mg film-coated Tablets  
 Atorvastatin 20mg film-coated Tablets  
 Atorvastatin 40mg film-coated Tablets  
 Atorvastatin 80mg film-coated Tablets |
| Name(s) of the active substance(s) (INN) | Atorvastatin calcium |
| Pharmacotherapeutic classification (ATC code) | HMG CoA reductase inhibitors (C10A A05) |
| Pharmaceutical form and strength(s) | Film-coated tablets 10mg, 20mg, 40mg, & 80mg |
| Reference numbers for the Mutual Recognition Procedure | UK/H/2381/01-04/DC |
| Reference Member State | United Kingdom |
| Member States concerned | DE |
| Marketing Authorisation Number(s) | PL 18179/0001-4 |
| Name and address of the authorisation holder | Midas Pharma GmbH  
 Rheinstrasse 49  
 Ingelheim  
 D-55218  
 Germany |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

Atorvastatin calcium (amorphous)

Nomenclature:
INN: Atorvastatin calcium
Chemical name: \( \text{[R-(R*, R*)]-2-(4-Fluorophenyl)-\(\beta,\delta,\)-dihydroxy-5-(1-methylethyl)-3 phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt(2:1)} \)

Structure:

\[ \text{C}_{68}\text{H}_{68}\text{CaF}_2\text{N}_4\text{O}_{10} \]

Molecular formula: \( \text{C}_{68}\text{H}_{68}\text{CaF}_2\text{N}_4\text{O}_{10} \)
Molecular weight: 1155.36 g/mol
CAS No: 134523-03-8
Physical form: White or off white powder
Solubility: Soluble in dimethyl sulphoxide
Polymorphism: Atorvastatin calcium exhibits polymorphism

The active substance, atorvastatin calcium, is not the subject of a European Pharmacopeia (Ph. Eur.) or British Pharmacopeia (B.P.) monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging, a low-density polyethylene (LDPE) bag, in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated by the active substance manufacturer for active substance stored in the proposed commercial packaging. Based on the data, a retest period of 5 years has been set, and is satisfactory.
**DRUG PRODUCT**

**Description and Composition**

Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets are presented as white, oblong, film-coated tablets containing 10mg, 20mg, 40mg, or 80mg of the active ingredient atorvastatin, as atorvastatin calcium. Full descriptions of the markings of the individual tablets may be found by referring to the SmPCs or patient information leaflet text.

Other ingredients consist of pharmaceutical excipients, namely butyl hydroxyanisole, ‘Prosolve SMCC90’ (consisting of microcrystalline cellulose and colloidal anhydrous silica), lactose monohydrate, sodium laurilsulfate, sodium hydrogen carbonate, crospovidone (Type A), magnesium stearate, and ‘Sinespum C’ (consisting of dimethicone 400, sucrose, sorbitan tristearate, macrogol 40 stearate, silica and 2-bromo-2-nitropropane-1,3-diol) making up the tablet core; and ‘Opadry OYL-28900 White’ making up the film coating. Opadry OYL-28900 White consists of lactose monohydrate, hydroxypropyl methylcellulose (hypromellose 15 CP), titanium dioxide (E171) and macrogol/PEG 4000. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Prosolve SMCC90, Sinespum C and Opadry Orange 03B23378, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop medicinal products bioequivalent and pharmaceutically equivalent to the reference products, Lipitor® 10mg, 20mg, 40mg and 80mg Tablets (PL 16051/0001-3 and 0005, Pfizer Ireland Pharmaceuticals).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

**Manufacture**

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and validation data provided for all the product strengths and were satisfactory.

**Finished product specification**

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been
described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for all strengths of the medicinal product. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The medicinal products are licensed for marketing in polyvinylchloride (PVC) / aluminium / polyamide / aluminium blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 10, 14, 28, 30, 50, 56 and 100 film-coated tablets (see SmPC for licensed pack sizes for individual licences). The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage instructions are ‘Store below 25°C’.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Atorvastatin 80mg film-coated Tablets, to the reference product, Lipitor® 80mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflet (PIL) and labelling texts are satisfactory. The MAH has submitted text versions only and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed. The PIL user testing report has been evaluated and is accepted.

**Conclusion**

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets from a pharmaceutical point of view.
III.2  NON-CLINICAL ASPECTS

Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of atorvastatin calcium, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Lipitor® 10mg, 20mg and 40mg Tablets (Pfizer Ireland Pharmaceuticals).

There are no objections to approval of Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets from a non-clinical point of view.

III.3  CLINICAL ASPECTS

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 cardiovascular disease

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

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of atorvastatin calcium is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of atorvastatin calcium is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.
Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Atorvastatin 80mg film-coated Tablets (test) and Lipitor® 80 mg film-coated tablets - Pfizer Ireland Pharmaceuticals (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products. The use of the 80mg strength only for the bioequivalence study has been adequately justified.

This was a comparative, controlled, balanced, randomised, two-period, two sequence, two-way, single-dose crossover bioequivalence study conducted in 72 healthy adult human subjects under fasting conditions. Following an overnight fast of 10 hours, a single dose of the investigational products was administered orally, with water, to each subject in each period. A satisfactory washout period of 14 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of atorvastatin were detected by a validated HPLC-MS/MS analytical method.

The primary pharmacokinetic parameters for this study were C_{max}, AUC_{0-t}, and AUC_{0-\infty}. Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed C_{max}, AUC_{0-t}, and AUC_{0-\infty}.

Results:

72 subjects were enrolled in the study, and all 72 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - 9 adverse events (headache, nausea, fever and muscle pain) were reported during the study in 6 subjects. None was serious: eight were classified as ‘moderate’ and one was classified as ‘mild’. Only 2 instances of headache and one of nausea were considered to be ‘possibly related’ to the study medication. All events resolved by the end of the study period. The adverse events that were reported were similar in the test and reference product arms of the study and are consistent with known data on atorvastatin. There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

<table>
<thead>
<tr>
<th>Test name</th>
<th>Parameter</th>
<th>Test value (T/R)</th>
<th>Lower 90% CL</th>
<th>Upper 90% CL</th>
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</thead>
<tbody>
<tr>
<td>Classic 90% Cl</td>
<td>AUC_{0-t}</td>
<td>102.582</td>
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<td>Classic 90% Cl</td>
<td>AUC_{0-inf}</td>
<td>102.061</td>
<td>96.001</td>
<td>108.503</td>
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<tr>
<td>Classic 90% Cl</td>
<td>C_{max}</td>
<td>97.054</td>
<td>85.548</td>
<td>110.107</td>
</tr>
</tbody>
</table>

Conclusion on Bioequivalence

The results of the bioequivalence study show that the 80mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for C_{max},
AUC₀₋₄, and AUC₀₋∞ fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Atorvastatin 10mg, 20mg and 40mg film-coated Tablets. As Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 80mg strength can be extrapolated to the 10mg, 20mg and 40mg strength tablets.

**Clinical efficacy**

No new data have been submitted and none are required. The UK reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of atorvastatin calcium is well-established from its extensive use in clinical practice.

**Clinical safety**

No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of atorvastatin calcium is well-known.

**PRODUCT INFORMATION:**

**Summary of Product Characteristics (SmPC)**

The approved SmPCs are consistent with those for the reference products, and are acceptable.

**Patient Information Leaflet**

The final PIL text is in line with the approved SmPCs and is satisfactory.

**Labelling**

The labelling text is satisfactory.

**Clinical overview**

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

**CONCLUSIONS**

For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Lipitor® 10mg, 20mg and 40mg Tablets (Pfizer Ireland Pharmaceuticals).

Sufficient clinical information has been submitted to support these applications. The risk-benefit of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Atorvastatin 10mg, 20mg, 40mg 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 benefit/risk 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 Atorvastatin 80mg film-coated Tablets, and the reference product, Lipitor® 80mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals).

As the proposed products, Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 80mg strength were extrapolated to the 10mg, 20mg and 40mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the UK reference products and are satisfactory.

The final PIL text is in line with the SmPCs. User testing of the leaflet text has been accepted based on a bridging report provided by the applicant making reference to the successful user-testing of the PIL texts for Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets [UK/H/1919, 2370, 2380/01-04/DC]. The bridging report is accepted.

The approved labelling texts are satisfactory.

The MAH has submitted text versions only for the PILs and labelling, and has committed to submitting mock-up livery to the relevant regulatory authorities for approval before packs are marketed.

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 and its conclusions support the claim that the applicant’s products, Atorvastatin 10mg, 20mg, 40mg and 80mg film-coated Tablets, and their respective reference products, Lipitor® 10mg, 20mg, 40mg and 80mg Tablets (Pfizer Ireland Pharmaceuticals), are interchangeable. Extensive clinical experience with atorvastatin calcium is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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