Public Assessment Report

Decentralised Procedure

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

Procedure No: UK/H/2166/001-4/DC

UK Licence No: PL 18866/0055-8

Rockspring Healthcare Limited
Lay Summary

On 02 November 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations to Rockspring Healthcare Limited for the medicinal products Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets (PL 18866/0055-8; UK/H/2166/001-4/DC). These are prescription-only medicines (POM) 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. Atorvastatin Tablets can also be used to reduce an increased risk of heart disease, even in patients with normal cholesterol levels. A standard cholesterol lowering diet should be maintained during treatment with Atorvastatin Tablets.

The active ingredient, atorvastatin (as atorvastatin calcium), belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets; outweigh the risks; hence Marketing Authorisations were granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure          Page 4
Module 2: Summary of Product Characteristics        Page 5
Module 3: Product Information Leaflet               Page 69
Module 4: Labelling                                  Page 75
Module 5: Scientific discussion                     Page 79

I Introduction
II About the product
III Scientific overview and discussion
   III 1 Quality aspects
   III 2 Non-clinical aspects
   III 3 Clinical aspects
IV Overall conclusion and benefit/risk assessment

Module 6: Steps taken after initial procedure
### Module 1

**Information about the initial procedure**

| Product Names | UK/H/2166/001/DC: Atorvastatin 10 mg Film-coated Tablets  
UK/H/2166/002/DC: Atorvastatin 20 mg Film-coated Tablets  
UK/H/2166/003DC: Atorvastatin 40 mg Film-coated Tablets  
UK/H/2166/004DC: Atorvastatin 80 mg Film-coated Tablets |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Type of Applications</strong></td>
<td>Generic, Article 10.1</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Atorvastatin calcium</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Film-coated tablets</td>
</tr>
<tr>
<td><strong>Strengths</strong></td>
<td>10 mg, 20 mg, 40 mg and 80mg</td>
</tr>
</tbody>
</table>
| **MA Holder** | Rockspring Healthcare Ltd  
38/40 Chamberlayne Road  
London, UK, NW10 3JE |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | UK/H/2166/001-4/DC: Austria, Germany, Spain, France, Italy, Luxembourg, the Netherlands, Poland and Portugal |
| **Procedure Number** | UK/H/2166/001-4/DC |
| **Timetable** | Day 210 – 29 September 2011 |
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).

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Atorvastatin 10 mg Film-coated Tablets are white to off-white, elliptic, biconvex, smooth tablets with dimensions 9.6 mm x 5.1 mm.

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

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

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

4.2 Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

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

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorvastatin 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**
Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

**Prevention of cardiovascular disease**
In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

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

**Hepatic impairment**
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).

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

**Paediatric use**

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

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

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

### 4.3 Contraindications
Atorvastatin is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

### 4.4 Special warnings and precautions for use

**Liver effects**
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin 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 coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).

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

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

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

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

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

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

Concomitant treatment with other medicinal products
Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, striperentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibric acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.
In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (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**
Developmental safety in the paediatric population has not been established (see section 4.8).

**Excipients**
Atorvastatin contains maltose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

**Effect of co-administered medicinal products on atorvastatin**

Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

**CYP3A4 inhibitors**

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

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

**CYP3A4 inducers**

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

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

**Gemfibrozil / fibric acid derivatives**

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

**Ezetimibe**

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

**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.

**Fusidic acid**

Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

**Effect of atorvastatin on co-administered medicinal products**

**Digoxin**

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

**Oral contraceptives**

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

**Warfarin**

In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin</th>
<th>Change in AUC</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tipranavir 500 mg BID/Ritonavir 200 mg BID, 8 days (days 14 to 21)</strong></td>
<td>40 mg on day 1, 10 mg on day 20</td>
<td>↑ 9.4 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td><strong>Ciclosporin 5.2 mg/kg/day, stable dose</strong></td>
<td>10 mg OD for 28 days</td>
<td>↑ 8.7 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Lopinavir 400 mg BID/Ritonavir 100 mg BID, 14 days</strong></td>
<td>20 mg OD for 4 days</td>
<td>↑ 5.9 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td><strong>Clarithromycin 500 mg BID, 9 days</strong></td>
<td>80 mg OD for 8 days</td>
<td>↑ 4.4 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Saquinavir 400 mg BID/Ritonavir 300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing</strong></td>
<td>40 mg OD for 4 days</td>
<td>↑ 3.9 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td><strong>Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days</strong></td>
<td>10 mg OD for 4 days</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Itraconazole 200 mg OD, 4 days</strong></td>
<td>40 mg SD</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Fosamprenavir 700 mg BID/Ritonavir 100 mg BID, 14 days</strong></td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.5 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Fosamprenavir 1400 mg BID, 14 days</strong></td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.3 fold</td>
<td></td>
</tr>
<tr>
<td><strong>Nelfinavir 1250 mg BID, 14 days</strong></td>
<td>10 mg OD for 28 days</td>
<td>↑ 1.7 fold</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td><strong>Grapefruit Juice, 240 mL OD</strong></td>
<td>40 mg, SD</td>
<td>↑ 37%</td>
<td>Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.</td>
</tr>
<tr>
<td><strong>Diltiazem 240 mg OD, 28 days</strong></td>
<td>40 mg, SD</td>
<td>↑ 51%</td>
<td>After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td><strong>Erythromycin 500 mg QID, 7 days</strong></td>
<td>10 mg, SD</td>
<td>↑ 33%</td>
<td>Lower maximum dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td><strong>Amlodipine 10 mg, single dose</strong></td>
<td>80 mg, SD</td>
<td>↑ 18%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td><strong>Cimetidine 300 mg QID, 2 weeks</strong></td>
<td>10 mg OD for 4 weeks</td>
<td>↓ less than 1%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td><strong>Antacid suspension of magnesium and</strong></td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Co-administered medicinal product and dosing regimen</td>
<td>Atorvastatin</td>
<td>Dose (mg)</td>
<td>Change in AUC &amp;</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-------------</td>
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<td>-----------------</td>
</tr>
<tr>
<td>aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg OD, 14 days</td>
<td></td>
<td>10 mg for 3 days</td>
<td>↓ 41%</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 7 days (co-administered)</td>
<td></td>
<td>40 mg SD</td>
<td>↑ 30%</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 5 days (doses separated)</td>
<td></td>
<td>40 mg SD</td>
<td>↓ 80%</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td></td>
<td>40 mg SD</td>
<td>↑ 35%</td>
</tr>
<tr>
<td>Fenofibrate 160 mg OD, 7 days</td>
<td></td>
<td>40 mg SD</td>
<td>↑ 3%</td>
</tr>
</tbody>
</table>

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

* See sections 4.4 and 4.5 for clinical significance.
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).
** Single sample taken 8-16 h post dose.
^ Total atorvastatin equivalent activity
Increase is indicated as “↑”, decrease as “↓”
OD = once daily; SD = single dose; BID = twice daily; QID = four times daily

<table>
<thead>
<tr>
<th>Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin and dosing regimen</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>80 mg OD for 10 days</td>
</tr>
<tr>
<td>40 mg OD for 22 days</td>
</tr>
<tr>
<td>80 mg OD for 15 days</td>
</tr>
</tbody>
</table>

* Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.
Increase is indicated as “↑”, decrease as “↓”
OD = once daily; SD = single dose

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

Women of childbearing potential

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

Pregnancy

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

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

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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

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

Infections and infestations:
Common: nasopharyngitis.

Blood and lymphatic system disorders:
Rare: thrombocytopenia.

Immune system disorders:
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders:
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia

Psychiatric disorders:
Uncommon: nightmare, insomnia.
Nervous system disorders:
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders:
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders:
Uncommon: tinnitus
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders:
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders:
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders:
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations:
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.

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

Elevated serum creatine kinase (CK) 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).

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

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

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

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

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

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.
Homozygous familial hypercholesterolaemia
In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

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

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

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

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

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

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

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

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

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

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

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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No. of Events (Atorvastatin vs Placebo)</th>
<th>Absolute Risk Reduction1 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major cardiovascular events</td>
<td>37%</td>
<td>83 vs. 127</td>
<td>3.2%</td>
<td>0.0010</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; CAGB = 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 ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

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

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

Paediatric Population

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

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

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

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

**Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old**

In a double-blind, placebo controlled study followed by an open-label phase, 187 boys and postmenarchal girls 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (FH) or severe hypercholesterolaemia were randomised to Atorvastatin (n=140) or placebo (n=47) for 26 weeks and then all received atorvastatin for 26 weeks. The dosage of atorvastatin (once daily) was 10 mg for the first 4 weeks and up-titrated to 20 mg if the LDL-C level
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

was >3.36 mmol/l. Atorvastatin significantly decreased plasma levels of total- C, LDL-C, triglycerides, and apolipoprotein B during the 26 week double-blind phase. The mean achieved LDL-C value was 3.38 mmol/l (range: 1.81-6.26 mmol/l) in the Atorvastatin group compared to 5.91 mmol/l (range: 3.93-9.96 mmol/l) in the placebo group during the 26- week double-blind phase.

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

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

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

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

5.2 Pharmacokinetic properties

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (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.

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

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

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

**Gender:** Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for 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 (Child-Pugh B).

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

5.3 **Preclinical safety data**
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

**Tablet core**
- 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.
Store in the original packaging in order to protect from moisture
6.5 Nature and contents of container
Aluminium-aluminium blisters consisting of Aluminium/PVC or PVDC - Poliamide/Aluminium/PVC. 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.

7 MARKETING AUTHORISATION HOLDER
Rockspring Healthcare Ltd
38/40 Chamberlayne Road
London, UK, NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL18866/0055

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/11/2011

10 DATE OF REVISION OF THE TEXT
02/11/2011
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).
Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
Atorvastatin 20 mg Film-coated Tablets are white to off-white, elliptic, biconvex, smooth tablets with dimensions 12.4 mm x 6.5 mm.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Hypercholesterolaemia
Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.
Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

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

4.2 Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.
The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.
The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorvastatin 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
Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Prevention of cardiovascular disease
In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

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

Hepatic impairment
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).

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

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

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

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

4.3 Contraindications
Atorvastatin is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use
Liver effects
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin 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 coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).
Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

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

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

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

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

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

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).
The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (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
Developmental safety in the paediatric population has not been established (see section 4.8).

Excipients
Atorvastatin contains maltose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

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

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

CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport protein inhibitors
Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).
**Gemfibrozil / fibric acid derivatives**
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

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

**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.

**Fusidic acid**
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

**Effect of atorvastatin on co-administered medicinal products**

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

**Oral contraceptives**
Co-administration of Atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

**Warfarin**
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin</th>
<th>Change in AUC</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipranavir 500 mg BID/Ritonavir 200 mg BID, 8 days (days 14 to 21)</td>
<td>40 mg on day 1, 10 mg on day 20</td>
<td>↑ 9.4 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Ciclosporin 5.2 mg/kg/day, stable dose</td>
<td>10 mg OD for 28 days</td>
<td>↑ 8.7 fold</td>
<td></td>
</tr>
<tr>
<td>Lopinavir 400 mg BID/Ritonavir 100 mg BID, 14 days</td>
<td>20 mg OD for 4 days</td>
<td>↑ 5.9 fold</td>
<td>In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID, 9 days</td>
<td>80 mg OD for 8 days</td>
<td>↑ 4.4 fold</td>
<td></td>
</tr>
<tr>
<td>Saquinavir 400 mg BID/Ritonavir 300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing</td>
<td>40 mg OD for 4 days</td>
<td>↑ 3.9 fold</td>
<td>In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg OD, 4 days</td>
<td>40 mg SD</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 700 mg BID/Ritonavir 100 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.5 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.3 fold</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir 1250 mg BID, 14 days</td>
<td>10 mg OD for 28 days</td>
<td>↑ 1.7 fold</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Grapefruit Juice, 240 mL OD *</td>
<td>40 mg, SD</td>
<td>↑ 37%</td>
<td>Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.</td>
</tr>
<tr>
<td>Diltiazem 240 mg OD, 28 days</td>
<td>40 mg, SD</td>
<td>↑ 51%</td>
<td>After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID, 7 days</td>
<td>10 mg, SD</td>
<td>↑ 33%</td>
<td>Lower maximum dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Amlodipine 10 mg, single dose</td>
<td>80 mg, SD</td>
<td>↑ 18%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Cimetidine 300 mg QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ less than 1%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Antacid suspension of magnesium and</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%</td>
<td>No specific recommendation.</td>
</tr>
</tbody>
</table>
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin</th>
<th>Change in AUCa</th>
<th>Clinical Recommendationb</th>
</tr>
</thead>
<tbody>
<tr>
<td>aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg OD, 14 days</td>
<td>10 mg for 3 days</td>
<td>↓ 41%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 7 days (co-administered)</td>
<td>40 mg SD</td>
<td>↑ 30%</td>
<td>If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 5 days (doses separated)</td>
<td>40 mg SD</td>
<td>↓ 80%</td>
<td>If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>40 mg SD</td>
<td>↑ 35%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Fenofibrate 160 mg OD, 7 days</td>
<td>40 mg SD</td>
<td>↑ 3%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
</tbody>
</table>

a Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).
b See sections 4.4 and 4.5 for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).
** Single sample taken 8-16 h post dose.
^ Total atorvastatin equivalent activity
Increase is indicated as “↑”, decrease as “↓”
OD = once daily; SD = single dose; BID = twice daily; QID = four times daily

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

<table>
<thead>
<tr>
<th>Atorvastatin and dosing regimen</th>
<th>Co-administered medicinal product</th>
<th>Change in AUCa</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg OD for 10 days</td>
<td>Digoxin 0.25 mg OD, 20 days</td>
<td>↑ 15%</td>
<td>Patients taking digoxin should be monitored appropriately.</td>
</tr>
<tr>
<td>40 mg OD for 22 days</td>
<td>Oral contraceptive OD, 2 months</td>
<td>↑ 28%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>80 mg OD for 15 days</td>
<td>Phenazone, 600 mg SD</td>
<td>↑ 3%</td>
<td>No specific recommendation.</td>
</tr>
</tbody>
</table>

a Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.
Increase is indicated as “↑”, decrease as “↓”
OD = once daily; SD = single dose

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

**Women of childbearing potential**

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

**Pregnancy**

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

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

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

**Breastfeeding**

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

**Fertility**

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

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

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 **Undesirable effects**

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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

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

**Infections and infestations:**

Common: nasopharyngitis.

**Blood and lymphatic system disorders:**

Rare: thrombocytopenia.

**Immune system disorders:**

Common: allergic reactions.

Very rare: anaphylaxis.

**Metabolism and nutrition disorders:**

Common: hyperglycaemia.

Uncommon: hypoglycaemia, weight gain, anorexia

**Psychiatric disorders:**

Uncommon: nightmare, insomnia.
Nervous system disorders:
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders:
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders:
Uncommon: tinnitus
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders:
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders:
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders:
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations:
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.

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

Elevated serum creatine kinase (CK) 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).

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

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

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

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

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

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

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

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

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

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

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

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

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

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

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

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

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

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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No. of Events (Atorvastatin vs Placebo)</th>
<th>Absolute Risk Reduction (%)</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>83 vs. 127</td>
<td>3.2%</td>
<td>0.0010</td>
</tr>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>38 vs 64</td>
<td>1.9%</td>
<td>0.0070</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>21 vs. 39</td>
<td>1.3%</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 ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

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

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

**Paediatric Population**

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

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

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

Mean values for LDL-C, TC, VLDL-C, and Apo B decreased by Week 2 among all subjects. For subjects whose dose was doubled, additional decreases were observed as early as 2 weeks, at the first assessment, after dose escalation. The mean percent decreases in lipid parameters were similar for both cohorts, regardless of whether subjects remained at their initial dose or doubled their initial dose. At Week 8, on average, the percent change from baseline in LDL-C and TC was approximately 40% and 30%, respectively, over the range of exposures.
**Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old**

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

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

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

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

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

### 5.2 Pharmacokinetic properties

**Absorption**
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C\text{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 ≥ 98% bound to plasma proteins.

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

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

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

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

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

### 5.3 Preclinical safety data

Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

### 6 PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

**Tablet core**
- 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.
Store in the original packaging in order to protect from moisture

6.5 Nature and contents of container
Aluminium-aluminium blisters consisting of Aluminium/PVC or PVDC - Poliamide/Aluminium/PVC.
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.

7 MARKETING AUTHORISATION HOLDER
Rockspring Healthcare Ltd
38/40 Chamberlayne Road
London, UK, NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL18866/0056

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZAION
02/11/2011

10 DATE OF REVISION OF THE TEXT
02/11/2011
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).

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Atorvastatin 40 mg Film-coated Tablets are white to off-white, elliptic, biconvex, smooth tablets with dimensions 15.5 mm x 8.2 mm.

4 CLINICAL PARTICULARS

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

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

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

4.2 Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

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

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorvastatin 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
Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Prevention of cardiovascular disease
In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

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

Hepatic impairment
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).

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

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

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

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

4.3 Contraindications
Atorvastatin is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use
Liver effects
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin 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 coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).
### Skeletal muscle effects

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

### Before the treatment

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

- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

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

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

### Creatine kinase measurement

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

### Whilst on treatment

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

### Concomitant treatment with other medicinal products

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicinal products that may increase the plasma concentration of atorvastatin such as potent inhibitors of CYP3A4 or transport proteins (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors including ritonavir, lopinavir, atazanavir, indinavir, darunavir, etc). The risk of myopathy may also be increased with the concomitant use of gemfibrozil and other fibril acid derivates, erythromycin, niacin and ezetimibe. If possible, alternative (non-interacting) therapies should be considered instead of these medicinal products.

In cases where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving medicinal products that increase the plasma concentration of atorvastatin, a lower maximum dose of atorvastatin is recommended. In addition, in the case of potent CYP3A4 inhibitors, a lower starting dose of atorvastatin should be considered and appropriate clinical monitoring of these patients is recommended (see section 4.5).
The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (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
Developmental safety in the paediatric population has not been established (see section 4.8).

Excipients
Atorvastatin contains maltose. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates and ezetimibe (see section 4.4).

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

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

CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations. The effect of rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant administration cannot be avoided, patients should be carefully monitored for efficacy.

Transport protein inhibitors
Inhibitors of transport proteins (e.g. ciclosporin) can increase the systemic exposure of atorvastatin (see Table 1). The effect of inhibition of hepatic uptake transporters on atorvastatin concentrations in hepatocytes is unknown. If concomitant administration cannot be avoided, a dose reduction and clinical monitoring for efficacy is recommended (see Table 1).
Gemfibrozil / fibric acid derivatives
The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored (see section 4.4).

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

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.

Fusidic acid
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Effect of atorvastatin on co-administered medicinal products

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

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

Warfarin
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin

<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin</th>
<th>Change in AUC</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipranavir 500 mg BID/Ritonavir 200 mg BID, 8 days (days 14 to 21)</td>
<td>40 mg on day 1, 10 mg on day 20</td>
<td>↑ 9.4 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Ciclosporin 5.2 mg/kg/day, stable dose</td>
<td>10 mg OD for 28 days</td>
<td>↑ 8.7 fold</td>
<td></td>
</tr>
<tr>
<td>Lopinavir 400 mg BID/Ritonavir 100 mg BID, 14 days</td>
<td>20 mg OD for 4 days</td>
<td>↑ 5.9 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID, 9 days</td>
<td>80 mg OD for 8 days</td>
<td>↑ 4.4 fold</td>
<td></td>
</tr>
<tr>
<td>Saquinavir 400 mg BID/Ritonavir 300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing</td>
<td>40 mg OD for 4 days</td>
<td>↑ 3.9 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg OD, 4 days</td>
<td>40 mg SD</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.5 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.3 fold</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir 1250 mg BID, 14 days</td>
<td>10 mg OD for 28 days</td>
<td>↑ 1.7 fold</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Grapefruit Juice, 240 mL OD *</td>
<td>40 mg, SD</td>
<td>↑ 37%</td>
<td>Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.</td>
</tr>
<tr>
<td>Diltiazem 240 mg OD, 28 days</td>
<td>40 mg, SD</td>
<td>↑ 51%</td>
<td>After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID, 7 days</td>
<td>10 mg, SD</td>
<td>↑ 33%</td>
<td>Lower maximum dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Amlodipine 10 mg, single dose</td>
<td>80 mg, SD</td>
<td>↑ 18%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Cimetidine 300 mg QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ less than 1%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Antacid suspension of magnesium and</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%</td>
<td>No specific recommendation.</td>
</tr>
</tbody>
</table>
### Table 2: Effect of atorvastatin on the pharmacokinetics of co-administered medicinal products

<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin Dose (mg)</th>
<th>Change in AUC*</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg OD, 14 days</td>
<td>10 mg for 3 days</td>
<td>↓ 41%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 7 days (co-administered)</td>
<td>40 mg SD</td>
<td>↑ 30%</td>
<td>If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>40 mg SD</td>
<td>↑ 35%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Fenofibrate 160 mg OD, 7 days</td>
<td>40 mg SD</td>
<td>↑ 3%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
</tbody>
</table>

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change). 
* See sections 4.4 and 4.5 for clinical significance. 
* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites). 
** Single sample taken 8-16 h post dose. 
^ Total atorvastatin equivalent activity 
Increase is indicated as “↑”, decrease as “↓” 
OD = once daily; SD = single dose; BID = twice daily; QID = four times daily

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

<table>
<thead>
<tr>
<th>Atorvastatin and dosing regimen</th>
<th>Co-administered medical product</th>
<th>Change in AUC*</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg OD for 10 days</td>
<td>Digoxin 0.25 mg OD, 20 days</td>
<td>↑ 15%</td>
<td>Patients taking digoxin should be monitored appropriately.</td>
</tr>
<tr>
<td>40 mg OD for 22 days</td>
<td>Oral contraceptive OD, 2 months norethindrone 1 mg ethinyl estradiol 35µg</td>
<td>↑ 28% ↑ 19%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>80 mg OD for 15 days</td>
<td>* Phenazone, 600 mg SD</td>
<td>↑ 3%</td>
<td>No specific recommendation</td>
</tr>
</tbody>
</table>

* Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change) 
* Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone. 
Increase is indicated as “↑”, decrease as “↓” 
OD = once daily; SD = single dose

**Paediatric population**

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

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines
Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

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

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

Infections and infestations:
Common: nasopharyngitis.

Blood and lymphatic system disorders:
Rare: thrombocytopenia.

Immune system disorders:
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders:
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia

Psychiatric disorders:
Uncommon: nightmare, insomnia.
Nervous system disorders:
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders:
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders:
Uncommon: tinnitus
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders:
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders:
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullos including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders:
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations:
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.

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

Elevated serum creatine kinase (CK) 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).

The following adverse events have been reported with some statins:
• Sexual dysfunction.
• Depression.
• Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
Paediatric Population
The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

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

5.1 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 very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

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

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality.
Homozygous familial hypercholesterolaemia
In a multicenter 8 week open-label compassionate-use study with an optional extension phase of variable length, 335 patients were enrolled, 89 of which were identified as homozygous familial hypercholesterolaemia patients. From these 89 patients, the mean percent reduction in LDL-C was approximately 20%. Atorvastatin was administered at doses up to 80 mg/day.

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

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

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

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

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

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

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

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

Prevention of cardiovascular disease
The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No. of Events (Atorvastatin vs Placebo)</th>
<th>Absolute Risk Reduction1 (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal CHD plus non-fatal MI</td>
<td>36%</td>
<td>100 vs. 154</td>
<td>1.1%</td>
<td>0.0005</td>
</tr>
<tr>
<td>Total cardiovascular events and revascularization procedures</td>
<td>20%</td>
<td>389 vs. 483</td>
<td>1.9%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>29%</td>
<td>178 vs 247</td>
<td>1.4%</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 anti-hypertensive 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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No. of Events (Atorvastatin vs Placebo)</th>
<th>Absolute Risk Reduction1 (%)</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>83 vs. 127</td>
<td>3.2%</td>
<td>0.0010</td>
</tr>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>38 vs 64</td>
<td>1.9%</td>
<td>0.0070</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>21 vs. 39</td>
<td>1.3%</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 ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

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

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

**Paediatric Population**

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

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

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

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

*Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old*

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

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

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

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

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

5.2 Pharmacokinetic properties

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (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.

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

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

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

**Gender:** Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for 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 (Child-Pugh B).

**SLC1B1 polymorphism:** Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
**Tablet core**
- 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.
Store in the original packaging in order to protect from moisture
6.5 Nature and contents of container
Aluminium-aluminium blisters consisting of Aluminium/PVC or PVDC - Poliamide/Aluminium/PVC. 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.

7 MARKETING AUTHORITYHOLDER
Rockspring Healthcare Ltd
38/40 Chamberlayne Road
London, UK, NW10 3JE

8 MARKETING AUTHORIZATION NUMBER(S)
PL18866/0057

9 DATE OF first AUTHORISATION/RENEWAL OF THE AUTHORIZATION
02/11/2011

10 DATE OF REVISION OF THE TEXT
02/11/2011
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).

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

Atorvastatin 80 mg Film-coated Tablets are white to off-white, elliptic, biconvex, smooth tablets with dimensions 18.7 mm x 10.2 mm.

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

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

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

4.2 Posology and method of administration
Posology
The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

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

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia
The majority of patients are controlled with Atorvastatin 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.

Homozygous 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
Only limited data are available (see section 5.1).

The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

Prevention of cardiovascular disease
In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

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

Hepatic impairment
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).

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

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

For patients aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day with titration up to 20 mg per day. Titration should be conducted according to the individual response and tolerability in paediatric patients. Safety information for paediatric patients treated with doses above 20 mg, corresponding to about 0.5 mg/kg, is limited.

There is limited experience in children between 6-10 years of age (see section 5.1). Atorvastatin is not indicated in the treatment of patients below the age of 10 years.

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

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

4.3 Contraindications
Atorvastatin is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medicinal product
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- during pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use
Liver effects
Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases of greater than 3 times the upper limit of normal (ULN) persist, reduction of dose or withdrawal of Atorvastatin 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 coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (TIA) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section 5.1).
Skeletal muscle effects
Atorvastatin, like other HMG-CoA reductase inhibitors, may in rare occasions affect the skeletal muscle and cause myalgia, myositis, and myopathy that may progress to rhabdomyolysis, a potentially life-threatening condition characterised by markedly elevated creatine kinase (CK) levels (> 10 times ULN), myoglobinaemia and myoglobinuria which may lead to renal failure.

Before the treatment
Atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A CK level should be measured before starting statin treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2)

In such situations, the risk of treatment should be considered in relation to possible benefit, and clinical monitoring is recommended.
If CK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

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

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

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

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

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (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
Developmental safety in the paediatric population has not been established (see section 4.8).

Excipients
Atorvastatin contains maltose. Patients with rare hereditary problems of fructose intolerance should not
take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin
Atorvastatin is metabolized by cytochrome P450 3A4 (CYP3A4) and is a substrate to transport
proteins e.g. the hepatic uptake transporter OATP1B1. Concomitant administration of medicinal
products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma
concentrations of atorvastatin and an increased risk of myopathy. The risk might also be increased at
concomitant administration of atorvastatin with other medicinal products that have a potential to induce
myopathy, such as fibric acid derivatives and ezetimibe (see section 4.4).

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

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

CYP3A4 inducers
Concomitant administration of atorvastatin with inducers of cytochrome P450 3A (e.g. efavirenz,
rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due
to the dual interaction mechanism of rifampin, (cytochrome P450 3A induction and inhibition of
hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with
rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has
been associated with a significant reduction in atorvastatin plasma concentrations. The effect of
rifampin on atorvastatin concentrations in hepatocytes is, however, unknown and if concomitant
administration cannot be avoided, patients should be carefully monitored for efficacy.

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

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

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

**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.

**Fusidic acid**
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

**Effect of atorvastatin on co-administered medicinal products**

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

**Oral contraceptives**
Co-administration of Atorvastatin with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol.

**Warfarin**
In a clinical study in patients receiving chronic warfarin therapy, coadministration of atorvastatin 80 mg daily with warfarin caused a small decrease of about 1.7 seconds in prothrombin time during the first 4 days of dosing which returned to normal within 15 days of atorvastatin treatment. Although only very rare cases of clinically significant anticoagulant interactions have been reported, prothrombin time should be determined before starting atorvastatin in patients taking coumarin anticoagulants and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of atorvastatin is changed or discontinued, the same procedure should be repeated. Atorvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.
**Table 1: Effect of co-administered medicinal products on the pharmacokinetics of atorvastatin**

<table>
<thead>
<tr>
<th>Co-administered medicinal product and dosing regimen</th>
<th>Atorvastatin</th>
<th>Change in AUC&lt;sup&gt;§&lt;/sup&gt;</th>
<th>Clinical Recommendation&lt;sup&gt;‡&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tipranavir 500 mg BID/Ritonavir 200 mg BID, 8 days (days 14 to 21)</td>
<td>40 mg on day 1, 10 mg on day 20</td>
<td>↑ 9.4 fold</td>
<td>In cases where coadministration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Ciclosporin 5.2 mg/kg/day, stable dose</td>
<td>10 mg OD for 28 days</td>
<td>↑ 8.7 fold</td>
<td></td>
</tr>
<tr>
<td>Lopinavir 400 mg BID/Ritonavir 100 mg BID, 14 days</td>
<td>20 mg OD for 4 days</td>
<td>↑ 5.9 fold</td>
<td>In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID, 9 days</td>
<td>80 mg OD for 8 days</td>
<td>↑ 4.4 fold</td>
<td></td>
</tr>
<tr>
<td>Saquinavir 400 mg BID/Ritonavir 300 mg BID from days 5-7, increased to 400 mg BID on day 8, days 5-18, 30 min after atorvastatin dosing</td>
<td>40 mg OD for 4 days</td>
<td>↑ 3.9 fold</td>
<td>In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Darunavir 300 mg BID/Ritonavir 100 mg BID, 9 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg OD, 4 days</td>
<td>40 mg SD</td>
<td>↑ 3.3 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.5 fold</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
<td>↑ 2.3 fold</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir 1250 mg BID, 14 days</td>
<td>10 mg OD for 28 days</td>
<td>↑ 1.7 fold&lt;sup&gt;^&lt;/sup&gt;</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Grapefruit Juice, 240 mL OD *</td>
<td>40 mg, SD</td>
<td>↑ 37%</td>
<td>Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.</td>
</tr>
<tr>
<td>Diltiazem 240 mg OD, 28 days</td>
<td>40 mg, SD</td>
<td>↑ 51%</td>
<td>After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID, 7 days</td>
<td>10 mg, SD</td>
<td>↑ 33%^&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Lower maximum dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Amlodipine 10 mg, single dose</td>
<td>80 mg, SD</td>
<td>↑ 18%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Cimetidine 300 mg QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ less than 1%^&lt;sup&gt;†&lt;/sup&gt;</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Antacid suspension of magnesium and</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%^&lt;sup&gt;†&lt;/sup&gt;</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Co-administered medicinal product and dosing regimen</td>
<td>Atorvastatin</td>
<td>Change in AUC</td>
<td>Clinical Recommendation</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg OD, 14 days</td>
<td>10 mg for 3 days</td>
<td>↓ 41%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 7 days (co-administered)</td>
<td>40 mg SD</td>
<td>↑ 30%</td>
<td>If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 5 days (doses separated)</td>
<td>40 mg SD</td>
<td>↓ 80%</td>
<td></td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>40mg SD</td>
<td>↑ 35%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
<tr>
<td>Fenofibrate 160 mg OD, 7 days</td>
<td>40mg SD</td>
<td>↑ 3%</td>
<td>Lower starting dose and clinical monitoring of these patients is recommended.</td>
</tr>
</tbody>
</table>

* Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i.e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

* See sections 4.4 and 4.5 for clinical significance.

* Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of medicinal products metabolized by CYP3A4. Intake of one 240 ml glass of grapefruit juice also resulted in a decreased AUC of 20.4% for the active orthohydroxy metabolite. Large quantities of grapefruit juice (over 1.2 l daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites).

** Single sample taken 8-16 h post dose.

^ Total atorvastatin equivalent activity

Increase is indicated as “↑”, decrease as “↓”

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

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

<table>
<thead>
<tr>
<th>Atorvastatin and dosing regimen</th>
<th>Co-administered medical product</th>
<th>Change in AUC</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>80 mg OD for 10 days</td>
<td>Digoxin 0.25 mg OD, 20 days</td>
<td>↑ 15%</td>
<td>Patients taking digoxin should be monitored appropriately.</td>
</tr>
<tr>
<td>40 mg OD for 22 days</td>
<td>Oral contraceptive OD, 2 months</td>
<td>↑ 28%</td>
<td>No specific recommendation.</td>
</tr>
<tr>
<td></td>
<td>norethindrone 1 mg, ethinyl estradiol 35µg</td>
<td>↑ 19%</td>
<td></td>
</tr>
<tr>
<td>80 mg OD for 15 days</td>
<td>* Phenzone, 600 mg SD</td>
<td>↑ 3%</td>
<td>No specific recommendation</td>
</tr>
</tbody>
</table>

* Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)

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

Increase is indicated as “↑”, decrease as “↓”

OD = once daily; SD = single dose

** Paediatric population**

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

Women of childbearing potential

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

Pregnancy

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

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

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

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Atorvastatin has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a mean period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo. Based on data from clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for Atorvastatin.

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

Infections and infestations:
Common: nasopharyngitis.

Blood and lymphatic system disorders:
Rare: thrombocytopenia.

Immune system disorders:
Common: allergic reactions.
Very rare: anaphylaxis.

Metabolism and nutrition disorders:
Common: hyperglycaemia.
Uncommon: hypoglycaemia, weight gain, anorexia

Psychiatric disorders:
Uncommon: nightmare, insomnia.
Nervous system disorders:
Common: headache.
Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.
Rare: peripheral neuropathy.

Eye disorders:
Uncommon: vision blurred.
Rare: visual disturbance.

Ear and labyrinth disorders:
Uncommon: tinnitus.
Very rare: hearing loss.

Respiratory, thoracic and mediastinal disorders:
Common: pharyngolaryngeal pain, epistaxis.

Gastrointestinal disorders:
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: cholestasis.
Very rare: hepatic failure.

Skin and subcutaneous tissue disorders:
Uncommon: urticaria, skin rash, pruritus, alopecia.
Rare: angioneurotic oedema, dermatitis bullous including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Musculoskeletal and connective tissue disorders:
Common: myalgia, arthralgia, pain in extremity, muscle spasms, joint swelling, back pain.
Uncommon: neck pain, muscle fatigue.
Rare: myopathy, myositis, rhabdomyolysis, tendonopathy, sometimes complicated by rupture.

Reproductive system and breast disorders:
Very rare: gynecomastia.

General disorders and administration site conditions
Uncommon: malaise, asthenia, chest pain, peripheral oedema, fatigue, pyrexia.

Investigations:
Common: liver function test abnormal, blood creatine kinase increased.
Uncommon: white blood cells urine positive.

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

Elevated serum creatine kinase (CK) 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).

The following adverse events have been reported with some statins:
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).
**Paediatric Population**

The clinical safety database includes safety data for 249 paediatric patients who received atorvastatin, among which 7 patients were < 6 years old, 14 patients were in the age range of 6 to 9, and 228 patients were in the age range of 10 to 17.

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

Based on the data available, frequency, type and severity of adverse reactions in children are expected to be the same as in adults. There is currently limited experience with respect to long-term safety in the paediatric population.

4.9 **Overdose**

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

5 **PHARMACOLOGICAL PROPERTIES**

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

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

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

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

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

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

Atherosclerosis

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

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

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

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomized, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.
Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137).

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

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

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>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>No. of Events (Atorvastatin vs Placebo)</th>
<th>Absolute Risk Reduction (%)</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>83 vs. 127</td>
<td>3.2%</td>
<td>0.0010</td>
</tr>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>38 vs 64</td>
<td>1.9%</td>
<td>0.0070</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>21 vs. 39</td>
<td>1.3%</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 ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years), and had an average baseline LDL of 133 mg/dL (3.4 mmol/L). The mean LDL-C was 73 mg/dL (1.9 mmol/L) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

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

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

**Paediatric Population**

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

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

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

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

**Heterozygous Familial Hypercholesterolaemia in Paediatric Patients aged 10-17 years old**

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

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

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

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

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

5.2 Pharmacokinetic properties

Absorption
Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C\text{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 ≥ 98% bound to plasma proteins.

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

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

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

**Gender:** Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for 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 (Child-Pugh B).

**SLC1B1 polymorphism:** Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the AUC0-24h reached in humans at the highest recommended dose) showed hepatocellular adenomas in males and hepatocellular carcinomas in females. There is evidence from animal experimental studies that HMG-CoA reductase inhibitors may affect the development of embryos or fetuses. In rats, rabbits and dogs atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses fetal toxicity was observed in rats and rabbits. The development of the rat offspring was delayed and post-natal survival reduced during exposure of the dams to high doses of atorvastatin. In rats, there is evidence of placental transfer. In rats, plasma concentrations of atorvastatin are similar to those in milk. It is not known whether atorvastatin or its metabolites are excreted in human milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

**Tablet core**
- 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.
Store in the original packaging in order to protect from moisture
6.5 Nature and contents of container
Aluminium-aluminium blisters consisting of Aluminium/PVC or PVDC - Poliamide/Aluminium/PVC.
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.

7 MARKETING AUTHORISATION HOLDER
Rockspring Healthcare Ltd
38/40 Chamberlayne Road
London, UK, NW10 3JE

8 MARKETING AUTHORISATION NUMBER(S)
PL18866/0058

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/11/2011

10 DATE OF REVISION OF THE TEXT
02/11/2011
Module 3

The leaflet text below is that agreed at the end of the Decentralised Procedure. The Marketing Authorisation Holder is required to submit the mock-up leaflet to the relevant regulatory authorities before marketing any pack size in a particular member state.

PACKAGE LEAFLET: INFORMATION FOR THE USER
Atorvastatin 10 mg Film-coated Tablets
Atorvastatin 20 mg Film-coated Tablets
Atorvastatin 40 mg Film-coated Tablets
Atorvastatin 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

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 this risk even if your cholesterol levels are normal. You should maintain a standard cholesterol lowering diet during treatment.

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 which affects the liver
- if you have had any unexplained abnormal liver tests at your last check
- if you are a woman able to have children and not using reliable contraception
- if you are pregnant or trying to become pregnant
- if you are breast-feeding.

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 had a previous stroke with bleeding into the brain, or have small pockets of fluid in the brain from previous strokes
- 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.

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

If any of these apply to you, your doctor will need to carry out a blood test before and possibly during your Atorvastatin Film-coated Tablets treatment to predict your risk of muscle-related side effects. The risk of muscle-related side effects e.g. rhabdomyolysis is known to increase when certain medicines are taken at the same time (see Section 2 “Taking other medicines”).

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 muscle-wasting condition known as rhabdomyolysis described in 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, telithromycin, ketoconazole, itraconazole, voriconazole, fluconazole, posaconazole, rifampin, fusidic acid
• Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid, derivatives, colestipol.
• Some calcium channel blockers used for angina or high blood pressure, e.g. amlodipine, diltiazem; medicines to regulate your heart rhythm, e.g. digoxin, verapamil, amiodarone
• Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, saquinavir, indinavir, darunavir, etc.
• Other medicines known to interact with Atorvastatin include ezetimibe (which lowers cholesterol), warfarin (which reduces blood clotting), oral contraceptives, stripentol (an anti-convulsant for epilepsy), cimetidine (used for heartburn and peptic ulcers), phenazine (a painkiller) and antacids (indigestion products containing aluminium or magnesium).
• Medicines obtained without a prescription: St John’s Wort.

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. Please note the following:

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.
Do not take Atorvastatin Film-coated Tablets if you are able to become pregnant unless you use reliable 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 proven.

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

Driving and using machines

 Normally this medicine does not affect your ability to drive or operate machines. However, 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.

Important information about some of the ingredients of Atorvastatin Film-coated Tablets

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE ATORVASTATIN FILM-COATED TABLETS

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 usual starting dose of Atorvastatin Film-coated Tablets is 10 mg once a day in adults and children aged 10 years or older. 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 for adults and 20 mg once daily for children.

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.

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 medicine or wish to stop your treatment, 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.

If you experience any of the following serious side effects, stop taking your tablets and tell your doctor immediately or go to the nearest hospital accident and emergency department.

Rare: affects 1 to 10 users in 10,000:
- Serious allergic reaction which causes swelling of the face, tongue and throat that can cause great difficulty in breathing.
- Serious illness with severe peeling and swelling of the skin, blistering of the skin, mouth, eyes, genitals and fever. Skin rash with pink-red blotches especially on palms of hands or soles of feet which may blister.
- Muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature it may be caused by an abnormal muscle breakdown which can be life-threatening and lead to kidney problems.

Very rare: affect less than 1 user in 10,000:
- If you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.

Other possible side effects with Atorvastatin Film-coated Tablets:

Common side effects (affects 1 to 10 users in 100) include:
- inflammation of the nasal passages, pain in the throat, nose bleed
- allergic reactions
- increases in blood sugar levels (if you have diabetes continue careful monitoring of your blood sugar levels), increase in blood creatine kinase
- headache
- nausea, constipation, wind, indigestion, diarrhoea
- joint pain, muscle pain and back pain
- blood test results that show your liver function can become abnormal.

Uncommon side effects (affects 1 to 10 users in 1000) include:
- anorexia (loss of appetite), weight gain, decreases in blood sugar levels (if you have diabetes you should continue careful monitoring of your blood sugar levels)
- having nightmares, insomnia
- dizziness, numbness or tingling in the fingers and toes, reductions of sensation to pain or touch, change in sense of taste, loss of memory
- blurred vision
- ringing in the ears and/or head
- vomiting, belching, abdominal pain upper and lower, pancreatitis (inflammation of the pancreas leading to stomach pain)
- hepatitis (liver inflammation)
- rash, skin rash and itching, hives, hair loss
- neck pain, muscle fatigue
- fatigue, feeling unwell, weakness, chest pain, swelling especially in the ankles (oedema), raised temperature
- urine tests that are positive for white blood cells.

Rare side effects (affects 1 to 10 users in 10,000) include:
- visual disturbance
- unexpected bleeding or bruising
- cholelithiasis (yellowing of the skin and whites of the eyes)
- tendon injury.
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

Very rare side effects (affects less than 1 user in 10,000) include:
- an allergic reaction - symptoms may include sudden wheezing and chest pain or tightness, swelling of the eyelids, face, lips, mouth, tongue or throat, difficulty breathing, collapse
- hearing loss
- gynecomastia (breast enlargement in men and women).

Possible side effects reported with some statins (medicines of the same type):
- Sexual difficulties
- Depression
- Breathing problems including persistent cough and/or shortness of breath or fever.

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.

Store below 30°C.
Store in the original packaging in order to protect from moisture.

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

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 is atorvastatin
  Each film-coated 10 mg tablet contains 10 mg of atorvastatin (as atorvastatin calcium)
  Each film-coated 20 mg tablet contains 20 mg of atorvastatin (as atorvastatin calcium)
  Each film-coated 40 mg tablet contains 40 mg of atorvastatin (as atorvastatin calcium)
  Each film-coated 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).

This medicine is available as 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets.

What Atorvastatin Film-coated Tablets looks like and contents of the pack
- Atorvastatin Film-coated Tablets are white to off-white, elliptic, biconvex, film-coated tablets.
- Atorvastatin Film-coated Tablets are available in Aluminium PVC or PVDC - Polyamide/Aluminium PVC blisters containing 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 96, 100 or 200 tablets. Not all pack sizes may be marketed.
Marketing Authorisation Holder and Manufacturer

**Marketing Authorisation Holder**
Rockspring Healthcare Ltd, 38/40 Chamberlayne Road
London, UK, NW10 3JE

**Manufacturer**
Teva Pharma, S.L.U. C/C, n. 4, Poligono Industrial Malpica, 50016 Zaragoza, Spain

TEVA Pharmaceutical Works Private Limited Company
Pallagi út 13, 4042 Debrecen
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Godollo, Tanacs Mihaly út 82
Hungary (Headquarters: 4042 Debrecen, Pallagi út 13)

TEVA UK Ltd
Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG
United Kingdom

Pharmachemie B.V.
Sweusweg 5, 2031 GA Haarlem
The Netherlands

TEVA Santé SA
Rue Bellocher, 89107 Sens
France

Teva Czech Industries s.r.o.
Ostravská 29, č.p. 305, 74770 Opava-Komárov
Czech Republic

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

<table>
<thead>
<tr>
<th>Name of Member State</th>
<th>Name of medicinal product</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Atorvastatin Film-coated Tablets</td>
</tr>
<tr>
<td>Austria</td>
<td>Atorock Filmtabtten</td>
</tr>
<tr>
<td>Germany</td>
<td>Atorock Filmtabtlette</td>
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<tr>
<td>Spain</td>
<td>Atorock Comprimido recubierto con película</td>
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<tr>
<td>France</td>
<td>ATORVASTATINE RATIOPHARM. comprimé pelliculé</td>
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<tr>
<td>Italy</td>
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<td>Poland &amp; Portugal</td>
<td>Atorock</td>
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This leaflet was last approved in September 2011.
Module 4
Labelling

Please note that the representative labelling text for Atorvastatin 10 mg Film-coated Tablets (PL 18866/0055; UK/H/2166/001/DC) is shown below. The labelling text details for Atorvastatin 20 mg, 40 mg and 80 mg Film-coated Tablets (PL 18866/0056-8; UK/H/2166/002-4/DC) are consistent with these labels, with the exception of the product name and the product licence number. The Marketing Authorisation Holder is required to submit mock-ups of the labelling to the relevant regulatory authorities before marketing any pack size in a particular member state.

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<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
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<tr>
<td>BLISTER (7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 or 200 film-coated tablets.)</td>
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</tbody>
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1. **NAME OF THE MEDICINAL PRODUCT**

Atorvastatin 10 mg Film-coated Tablets

Atorvastatin

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

Rockspring Healthcare Ltd

3. **EXPIRY DATE**

EXP:

4. **BATCH NUMBER**

Batch:

5. **OTHER**
1. **NAME OF THE MEDICINAL PRODUCT**

Atorvastatin 10 mg Film-coated Tablets

Atorvastatin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

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

3. **LIST OF EXCIPIENTS**

Also contains maltose. See package leaflet for further information.

4. **PHARMACEUTICAL FORM AND CONTENTS**

<table>
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<th>7 film-coated tablets</th>
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<tr>
<td>10 film-coated tablets</td>
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<td>100 film-coated tablets</td>
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<td>200 film-coated tablets</td>
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5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.

Oral use

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

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Store in the original packaging in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MA Holder:
Rockspring Healthcare Ltd
38/40 Chamberlayne Road
London, UK, NW10 3JE

12. MARKETING AUTHORISATION NUMBER(S)

PL18866/0055

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

atorvastatin 10 mg Film-coated Tablets
Module 5
Scientific discussion during initial procedure

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets (PL 18866/0055-8; UK/H/2166/001-4/DC) could be approved. The products are prescription-only medicines (POM) used to treat:

- Hypercholesterolaemia
  Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.
  Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

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

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Germany, Spain, France, Italy, Luxembourg, the Netherlands, Poland and Portugal as Concerned Member States (CMS). These applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Lipitor 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets (Pfizer Ireland Pharmaceuticals, Ireland), which were first authorised in the UK on 07 November 1996.

Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets contain the active ingredient atorvastatin (as atorvastatin calcium). Atorvastatin is a competitive 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitor that reduces blood lipid concentrations.

No new non-clinical data have been submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use for over 10 years.

One single-dose, bioequivalence study was submitted to support these applications, comparing the test product Atorvastatin 80 mg Film-coated Tablets (Rockspring Healthcare Limited, UK) versus the reference product Zarator 80 mg film-coated tablets (Parke Davis SL (Grupo Pfizer), Spain). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical data were submitted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been in clinical use 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 Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of these products. 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.

The RMS and CMS considered that the applications could be approved at the end of procedure (Day 210) on 29 September 2011. After a subsequent national phase, licences were granted in the UK on 02 November 2011.
## ABOUT THE PRODUCT

| Name of the products in the Reference Member State | UK/H/2166/001/DC: Atorvastatin 10 mg Film-coated Tablets  
UK/H/2166/002/DC: Atorvastatin 20 mg Film-coated Tablets  
UK/H/2166/003DC: Atorvastatin 40 mg Film-coated Tablets  
UK/H/2166/004DC: Atorvastatin 80 mg Film-coated Tablets |
<table>
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<tr>
<td>Name(s) of the active substance (INN)</td>
<td>Atorvastatin calcium</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Lipid modifying agents, HMG-CoA-reductase inhibitors (ATC code: C10AA05)</td>
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<tr>
<td>Pharmaceutical form and strength(s)</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 18866/0055-8</td>
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| Name and address of the authorisation holder    | Rockspring Healthcare Ltd 38/40 Chamberlayne Road  
London, UK, NW10 3JE                                |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCE

INN: Atorvastatin calcium
Chemical Name: \([\text{R-}(R^*, R^*)]^-2-(4-\text{Fluorophenyl})-\beta,\beta,\delta,\delta,-\text{dihydroxy}-5-(1-\text{methylethyl})-3\text{phenyl}-4-\{(\text{phenylamino})\text{carbonyl}\}-1\text{H}-\text{pyrrole}-1\text{-heptanoic acid, calcium salt}(2:1)\).
Molecular formula: \(\text{C}_{66}\text{H}_{68}\text{CaF}_{2}\text{N}_{4}\text{O}_{10}\)
Structure:

Molecular mass: 1155.36
Appearance: A white to off-white coloured powder, soluble in water (about 0.5mg/ml), freely soluble in dimethyl sulfoxide, soluble in methanol, very slightly soluble in 95% ethanol and, practically insoluble in acetonitrile and diethyl ether.

Atorvastatin calcium is not the subject of a European Pharmacopoeia 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 specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

DRUG PRODUCT

Other Ingredients
Other ingredients consist of the pharmaceutical excipients in the tablet core and film coating, namely microcrystalline cellulose, sodium carbonate anhydrous, maltose, croscarmellose sodium, magnesium stearate, hypromellose (E464), hydroxypropylcellulose, triethyl citrate
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg Film-coated Tablets

(E1505), polysorbate 80 and titanium dioxide (E171). Appropriate justifications for the inclusion of each excipient have been provided.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of maltose and hydroxypropylcellulose which are controlled to National Formulary specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

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

Pharmaceutical Development
The objective of the development programme was to formulate safe, efficacious, stable products that could be considered generic medicinal products of the reference products Lipitor 10 mg, 20 mg, 40 mg and 80 mg Film-coated (Pfizer Ireland Pharmaceuticals, Ireland).

Suitable pharmaceutical development data have been provided for these applications.

Comparative in-vitro dissolution and impurity profiles have been provided for these products and their respective reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of all strengths of the product, along with an appropriate account of the manufacturing process. Based on pilot-scale batches, the manufacturing process has been validated and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation on future full-scale (commercial) batches.

Control of Finished Product
The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The tablets are packaged in aluminium/polyvinylchloride or polvinylidene chloride-poliamide/aluminium/polyvinylchloride blisters, in pack sizes of 7, 10, 14, 15, 28, 30, 50, 50x1, 56, 60, 84, 90, 98, 100 and 200 film-coated tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Directive 2002/72/EC, as amended) concerning materials in contact with foodstuff.

Stability
Finished product stability studies were performed in accordance with current guidelines on batches 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. Store in the original packaging in order to protect from moisture.”

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically satisfactory. Final text versions of the labelling and PIL have been provided. The Marketing Authorisation Holder has committed to submitting mock-ups to the relevant regulatory authorities for approval before marketing any pack size.

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.

MAA Forms
The MAA forms are satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin calcium are well-known, no further non-clinical studies are required and none have been provided.

NON-CLINICAL EXPERT REPORT
The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As these products are intended for generic substitution with products that are already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of Marketing Authorisations is recommended.
III.3 CLINICAL ASPECTS

The clinical pharmacology of atorvastatin calcium is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamic or pharmacokinetic data are provided or required for these applications.

In support of the applications, the Marketing Authorisation Holder submitted the following bioequivalence study:

A randomised, single-dose, two-treatment, two-sequence, two-period, crossover study comparing the pharmacokinetics of the test product Atorvastatin 80 mg Film-coated Tablets (Rockspring Healthcare Limited, UK) and the reference product Zarator 80 mg Tablets (Parke Davis SL (Grupo Pfizer), Spain) in healthy male and female adult subjects under fasting conditions.

The subjects were given a single dose of either treatment with 240ml of water after at least a 10-hour overnight fast; the subject were then fasted for a further 5 hours after dosing. Blood samples were collected before and up to 48 hours after each administration. The washout period between the treatment arms was 7 days. The parent drug and the active metabolite were used to demonstrate bioequivalence. The pharmacokinetic results are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic means, ratios and confidence intervals [CI]) of atorvastatin (parent)</th>
<th>Atorvastatin 80 mg (Test)</th>
<th>Zarator 80 mg (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (h*ng/ml)</td>
<td>161.08±70.25</td>
<td>155.00±70.53</td>
<td>1.04</td>
<td>0.96-1.14</td>
</tr>
<tr>
<td>AUC0-inf (h*ng/ml)</td>
<td>166.47±70.37</td>
<td>162.85±68.88</td>
<td>1.02</td>
<td>0.93-1.11</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>40.70±19.36</td>
<td>39.69±18.06</td>
<td>1.01</td>
<td>0.89-1.15</td>
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</tbody>
</table>

AUC0-t = area under the plasma concentration-time curve from time zero to t hours
AUC0-inf = area under the plasma concentration-time curve from time zero to infinity
Cmax = maximum plasma concentration
Ratios and 90% CI calculated from log-transformed data

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters (arithmetic means, ratios and confidence intervals [CI]) of ortho-hydroxy-atorvastatin (active metabolite)</th>
<th>Atorvastatin 80 mg (Test)</th>
<th>Zarator 80 mg (Reference)</th>
<th>Test/Ref Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-t (h*ng/ml)</td>
<td>235.56±97.52</td>
<td>241.57±103.89</td>
<td>0.98</td>
<td>0.90-1.08</td>
</tr>
<tr>
<td>AUC0-inf (h*ng/ml)</td>
<td>241.86±97.49</td>
<td>248.26±103.62</td>
<td>0.98</td>
<td>0.90-1.07</td>
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<tr>
<td>Cmax (ng/ml)</td>
<td>35.88±17.50</td>
<td>37.75±21.29</td>
<td>0.97</td>
<td>0.83-1.14</td>
</tr>
</tbody>
</table>

AUC0-t = area under the plasma concentration-time curve from time zero to t hours
AUC0-inf = area under the plasma concentration-time curve from time zero to infinity
Cmax = maximum plasma concentration
Ratios and 90% CI calculated from log-transformed data
The Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) defines the confidence limits for ratio of geometric means for acceptance of bioequivalence as 80% to 125% for \( C_{\text{max}} \) and AUC values. The 90% confidence intervals of the test/reference ratio of geometric means for AUC\(_{0-t} \), AUC\(_{0-\text{inf}} \) and \( C_{\text{max}} \) lie within the acceptable limits. Thus, the data support the claim that the test product Atorvastatin 80 mg Film-coated Tablets (Rockspring Healthcare Limited, UK) is bioequivalent to the reference product Zarator 80mg film-coated tablets (Parke Davis SL (Grupo Pfizer), Spain).

As the Spanish product used in the bioequivalence study is considered identical to the UK reference product (Lipitor 80 mg Film-coated tablets), bioequivalence has also been shown between the test product and the UK reference product.

As the 10 mg, 20 mg, 40 mg and 80 mg strength products meet all the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) for (bio) waiver, the results and conclusions from the bioequivalence study with the 80 mg tablet strength can be extrapolated to the 10 mg, 20 mg and 40 mg tablet strengths.

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

**SAFETY**  
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues arose during the bioequivalence study.

**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.

Suitable justification has been provided for not submitting a Risk Management Plan for these generic products.

**SUMMARIES OF PRODUCT CHARACTERISTICS (SmPCs), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING**  
The SmPCs, PIL and labelling are clinically acceptable. The SmPCs are consistent with those for the originator products. The PIL is consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with the current guidelines.

**CLINICAL EXPERT REPORT**  
The clinical overview is 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 quality characteristics of Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of atorvastatin are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s 80 mg strength tablet and the reference product Zarator 80 mg Tablets (Pfizer, Spain). As the 10 mg, 20 mg, 40 mg and 80 mg strengths of the product meet all the criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), for (bio) waiver, the results and conclusions from the bioequivalence study with the 80 mg tablet strength can be extrapolated to the 10 mg, 20 mg and 40 mg tablet strengths.

SAFETY
With the exception of the safety data from the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of atorvastatin calcium is well known, no additional safety data were required. No new or unexpected safety concerns arose from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with atorvastatin calcium is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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