Public Assessment Report

Decentralised Procedure

Atorvastatin 10 mg film-coated tablets
Atorvastatin 20 mg film-coated tablets
Atorvastatin 40 mg film-coated tablets

PL 14017/0198
PL 14017/0199
PL 14017/0200

UK/H/3430/001/DC
UK/H/3430/002/DC
UK/H/3430/003/DC

Dexcel-Pharma Ltd.
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Dexcel®-Pharma Ltd. Marketing Authorisations (licences) for the medicinal products Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets (product licence numbers: PL 14017/0198-0200) on 12 September 2011. These medicines are available on prescription only.

Atorvastatin tablets belong to a group of medicines known as statins. Statins lower blood cholesterol (and triglycerides). Atorvastatin tablets are recommended when a low-fat diet and lifestyle changes have not been adequate to lower blood cholesterol sufficiently. In people at increased risk of heart disease, Atorvastatin tablets may also be used to reduce such risk, even if blood cholesterol is normal. A standard cholesterol-lowering diet should be maintained during treatment.

The data submitted in support of these applications for Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information about Decentralised Procedure

<table>
<thead>
<tr>
<th>Name of the products in the Reference Member State</th>
<th>Atorvastatin 10 mg film-coated tablets Atorvastatin 20 mg film-coated tablets Atorvastatin 40 mg film-coated tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of applications</td>
<td>Generic (Article 10.1)</td>
</tr>
<tr>
<td>Name of the active substance (INN)</td>
<td>Atorvastatin</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Lipid modifying agents, HMG-CoA-reductase inhibitors (C10AA05)</td>
</tr>
<tr>
<td>Pharmaceutical form and strengths</td>
<td>Film-coated tablets; 10 mg, 20 mg and 40 mg</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/3430/001/DC UK/H/3430/002/DC UK/H/3430/003/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>UK</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>DE, FR, IE</td>
</tr>
<tr>
<td>Start of Decentralised Procedure</td>
<td>30 September 2010</td>
</tr>
<tr>
<td>End date of Decentralised Procedure</td>
<td>10 August 2011</td>
</tr>
<tr>
<td>Marketing Authorisation numbers</td>
<td>PL 14017/0198 PL 14017/0199 PL 14017/0200</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Dexcel®-Pharma Ltd. 7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK</td>
</tr>
</tbody>
</table>
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 hemi-hydrate.

Excipients:
Each Atorvastatin 10 mg film-coated tablet contains 28.90 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
10 mg: White, round, film coated tablet.

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*

MHRA PAR; ATORVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS, PL 14017/0198-0200
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. ciclosporin, 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.

Excipients

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

Paediatric use

Developmental safety in the paediatric population has not been established (see section 4.8).

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------</td>
</tr>
<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>
</tr>
<tr>
<td>Ciclosporin 5.2 mg/kg/day, stable dose</td>
<td>10 mg OD for 28 days</td>
</tr>
<tr>
<td>Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days</td>
<td>20 mg OD for 4 days</td>
</tr>
<tr>
<td>Clarithromycin 500 mg BID, 9 days</td>
<td>80 mg OD for 8 days</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>
</tr>
<tr>
<td>Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days</td>
<td>10 mg OD for 4 days</td>
</tr>
<tr>
<td>Itraconazole 200 mg OD, 4 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg BID, 14 days</td>
<td>10 mg OD for 4 days</td>
</tr>
<tr>
<td>Nelfinavir 1250 mg BID, 14 days</td>
<td>10 mg OD for 28 days</td>
</tr>
<tr>
<td>Grapefruit Juice, 240 mL OD *</td>
<td>40 mg, SD</td>
</tr>
<tr>
<td>Medicine</td>
<td>Dose (co-administered)</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Diltiazem 240 mg OD, 28 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Erythromycin 500 mg QID, 7 days</td>
<td>10 mg SD</td>
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<tr>
<td>Amlodipine 10 mg, single dose</td>
<td>80 mg SD</td>
</tr>
<tr>
<td>Cimetidine 300 mg QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
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<tr>
<td>Autacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
</tr>
<tr>
<td>Efavirenz 600 mg OD, 14 days</td>
<td>10 mg for 3 days</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 7 days (co-administered)</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Rifampin 600 mg OD, 5 days (doses separated)</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Gemfibrozil 600 mg BID, 7 days</td>
<td>40 mg SD</td>
</tr>
<tr>
<td>Fenofibrate 160 mg OD, 7 days</td>
<td>40 mg SD</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).
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>Medicinal product/Dose (mg)</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>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral contraceptive OD, 2 months</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- norethindrone 1 mg</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>- ethinyl estradiol 35 μg</td>
<td></td>
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<td></td>
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<tr>
<td>40 mg OD for 22 days</td>
<td></td>
<td></td>
<td></td>
<td></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>
<td></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 in 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 event profile for Atorvastatin.

Estimated frequencies of events 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).

<table>
<thead>
<tr>
<th>Infections and infestations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: nasopharyngitis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare: thrombocytopenia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: allergic reactions.</td>
</tr>
<tr>
<td>Very rare: anaphylaxis.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: hyperglycaemia.</td>
</tr>
<tr>
<td>Uncommon: hypoglycaemia, weight gain, anorexia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: nightmare, insomnia.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: headache.</td>
</tr>
<tr>
<td>Uncommon: dizziness, paraesthesia, hypoesthesia, dysgeusia, amnesia.</td>
</tr>
<tr>
<td>Rare: peripheral neuropathy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: vision blurred.</td>
</tr>
<tr>
<td>Rare: visual disturbance.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ear and labyrinth disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: tinnitus</td>
</tr>
<tr>
<td>Very rare: hearing loss.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: pharyngolaryngeal pain, epistaxis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.</td>
</tr>
<tr>
<td>Uncommon: vomiting, abdominal pain upper and lower, eructation, pancreatitis.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon: hepatitis.</td>
</tr>
<tr>
<td>Rare: cholestasis.</td>
</tr>
<tr>
<td>Very rare: hepatic failure.</td>
</tr>
</tbody>
</table>
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: gynaecomastia.

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 kinase 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-methylglutaryl-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.

**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 randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of 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-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD plus non-CVD</td>
<td>36%</td>
<td>100 vs. 154</td>
<td>1.1%</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
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>
</tbody>
</table>
Strokes (Fatal and non-fatal) | 48% | 21 vs 39 | 1.3% | 0.0163

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

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

Recurrence of 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 (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, the medicinal product does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special populations**

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

- **Paediatric**: 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 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).

- **SLOC1B1 polymorphism**: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLC01B1 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**

*Core:*
- Starch, pregelatinised
- Lactose monohydrate
- Crospovidone
- Hydroxypropylcellulose
- Silica, colloidal anhydrous
- Magnesium stearate

*White film-coating (Opadry II White OY-L-28900) containing:*
- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E-171)
- Macrogol 4000

*Polishing:*
- Carnauba wax

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.
6.5 Nature and contents of container
Atorvastatin Tablets are available in blister packs containing 28 film-coated tablets.
The tablets are packed in blisters made of PVC/OPA-coated Aluminium strips sealed with aluminium foil.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Dexcel®-Pharma Ltd.
7 Sopwith Way,
Drayton Fields,
Daventry,
Northamptonshire,
NN11 8PB, UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 14017/0198

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
12/09/2011

10 DATE OF REVISION OF THE TEXT
12/09/2011
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 hemi-hydrate.

Excipients:
Each Atorvastatin 20 mg film-coated tablet contains 57.80 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
20 mg: White, round, film coated tablet.

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. ciclosporin, 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.

Excipients

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

Paediatric use

Developmental safety in the paediatric population has not been established (see section 4.8).

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>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>Change in AUC ( &amp; )</td>
</tr>
</tbody>
</table>

MHRA PAR; ATORVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS, PL. 14017/0198-0200
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Details</th>
<th>Fold Increase</th>
<th>Notes</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</td>
</tr>
<tr>
<td>Drug Description</td>
<td>Dosage</td>
<td>% Change</td>
<td>Recommendation</td>
</tr>
<tr>
<td>------------------</td>
<td>--------</td>
<td>----------</td>
<td>----------------</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 aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%</td>
<td>No specific recommendation.</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
* 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 AUC &amp;</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 35 μg</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 “↓”

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 in 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 event profile for Atorvastatin.

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

**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: gynaecomastia.

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 kinase 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.

**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 randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of 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-</td>
<td>36%</td>
<td>100 vs. 154</td>
<td>1.1%</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

MHRA PAR; ATORVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS, PL 14017/0198-0200
Fatal MI
Total cardiovascular events and revascularization procedures
Total coronary events

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

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

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

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>
</tbody>
</table>
Recurrence of 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_{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, the medicinal product does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

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

- Paediatric: 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 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).

- SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.
5.3 **Preclinical safety data**
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the 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**
*Core:*
- Starch, pregelatinised
- Lactose monohydrate
- Crospovidone
- Hydroxypropylcellulose
- Silica, colloidal anhydrous
- Magnesium stearate

*White film-coating (Opadry II White OY-L-28900) containing:*
- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E-171)
- Macrogol 4000

*Polishing:*
- Carnauba wax

6.2 **Incompatibilities**
Not applicable

6.3 **Shelf life**
2 years

6.4 **Special precautions for storage**
Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 **Nature and contents of container**
Atorvastatin Tablets are available in blister packs containing 28 film-coated tablets. The tablets are packed in blisters made of PVC/OPA-coated Aluminium strips sealed with aluminium foil.

6.6 Special precautions for disposal
No special requirements

7 MARKETING AUTHORISATION HOLDER
Dexcel®-Pharma Ltd.
7 Sopwith Way,
Drayton Fields,
Daventry,
Northamptonshire,
NN11 8PB, UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 14017/0199

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHOURISATION
12/09/2011

10 DATE OF REVISION OF THE TEXT
12/09/2011
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 hemi-hydrate.

Excipients:
Each Atorvastatin 40 mg film-coated tablet contains 115.60 mg lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
40 mg: White, capsule-shaped, film coated tablet.

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. ciclosporin, 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.

Excipients

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

Paediatric use

Developmental safety in the paediatric population has not been established (see section 4.8).

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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
</tr>
<tr>
<td></td>
<td>Change in AUC</td>
</tr>
<tr>
<td></td>
<td>Clinical Recommendation</td>
</tr>
</tbody>
</table>

MHRA PAR; ATORVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS, PL 14017/0198-0200
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Atorvastatin Dose</th>
<th>Change in LDL-C</th>
<th>Note</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, do not exceed 10 mg atorvastatin daily. 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 20 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</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Change</td>
<td>Recommendation</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Diltiazem 240 mg OD, 28 days</td>
<td>40 mg</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</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</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 aluminium hydroxides, 30 mL QID, 2 weeks</td>
<td>10 mg OD for 4 weeks</td>
<td>↓ 35%</td>
<td>No specific recommendation.</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>

* 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 medicinal product</th>
<th>Medicinal product/Dose (mg)</th>
<th>Change in AUC &amp;</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>
<td></td>
</tr>
<tr>
<td>40 mg OD for 22 days</td>
<td>Oral contraceptive OD, 2 months: 1 mg norethindrone, 35 μg ethinyl estradiol</td>
<td>↑ 28% ↑ 19%</td>
<td>No specific recommendation.</td>
<td></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>
<td></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 in 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 event profile for Atorvastatin.

Estimated frequencies of events 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:

Reproductive system and breast disorders:
Very rare: gynaecomastia.

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 kinase 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-methylglutaryl-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.

**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 randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis.

The median percent change, from baseline, in total atheroma volume (the primary study criteria) was -0.4% (p=0.98) in the atorvastatin group and +2.7% (p=0.001) in the pravastatin group (n=249). When compared to pravastatin the effects of 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-</td>
<td>36%</td>
<td>100 vs. 154</td>
<td>1.1%</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

MHRA PAR; ATORVASTATIN 10 MG, 20 MG AND 40 MG FILM-COATED TABLETS, PL 14017/0198-0200
Fatal MI
Total cardiovascular events and revascularization procedures

<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>
</tbody>
</table>

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

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

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

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

The absolute and relative risk reduction effect of atorvastatin was as follows:
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 \( \geq 4 \) mmol/L. A total of 39 children and adolescents, 6 to 17 years of age, were enrolled. Cohort A included 15 children, 6 to 12 years of age and at Tanner Stage 1. Cohort B included 24 children, 10 to 17 years of age and at Tanner Stage \( \geq 2 \).

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

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

*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, the medicinal product does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special populations**

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

- **Paediatric:** 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 C\text{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\text{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

- **SLOC1B1 polymorphism:** Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.
5.3 Preclinical safety data
Atorvastatin was negative for mutagenic and clastogenic potential in a battery of 4 in vitro tests and 1 in vivo assay. Atorvastatin was not found to be carcinogenic in rats, but high doses in mice (resulting in 6-11 fold the 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
Core:
- Starch, pregelatinised
- Lactose monohydrate
- Crospovidone
- Hydroxypropylcellulose
- Silica, colloidal anhydrous
- Magnesium stearate

White film-coating (Opadry II White OY-L-28900) containing:
- Lactose monohydrate
- Hypromellose
- Titanium dioxide (E-171)
- Macrogol 4000

Polishing:
- Carnauba wax

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.
6.5 **Nature and contents of container**
Atorvastatin Tablets are available in blister packs containing 28 film-coated tablets.
The tablets are packed in blisters made of PVC/OPA-coated Aluminium strips sealed with aluminium foil.

6.6 **Special precautions for disposal**
No special requirements

7 **MARKETING AUTHORISATION HOLDER**
Dexcel®-Pharma Ltd.
7 Sopwith Way,
Drayton Fields,
Daventry,
Northamptonshire,
NN11 8PB, UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 14017/0200

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
12/09/2011

10 **DATE OF REVISION OF THE TEXT**
12/09/2011
Atorvastatin 10 mg film-coated tablets
Atorvastatin 20 mg film-coated tablets
Atorvastatin 40 mg film-coated tablets

Atorvastatin

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

In this leaflet:
1. What Atorvastatin Tablets are and what are they used for
2. Before you take Atorvastatin Tablets
3. How to take Atorvastatin Tablets
4. Possible side effects
5. How to store Atorvastatin Tablets
6. Further information

1. WHAT ATORVASTATIN TABLETS ARE AND WHAT ARE THEY USED FOR
Atorvastatin Tablets belong to a group of medicines known as statins. Statins lower blood cholesterol (and triglycerides).

Atorvastatin Tablets are advised when a low-fat diet and lifestyle changes have not been adequate to lower blood cholesterol as recommended.

If you are at an increased risk of heart disease, Atorvastatin Tablets may also be used to reduce such risk even if your blood cholesterol is "normal". You should maintain a standard cholesterol-lowering diet during treatment.

2. BEFORE YOU TAKE ATORVASTATIN TABLETS
Do not take Atorvastatin Tablets if you
- are hypersensitive (allergic) to Atorvastatin Tablets or to any similar medicines used to lower blood cholesterol or to any of the other ingredients of the medicine – see Section 6 for details
- have or have ever had a disease that affects the liver
- have had any unexplained abnormal blood tests for liver function
- are a woman able to have children and not using reliable contraception
- are pregnant or trying to become pregnant
- are breast-feeding

Take special care with Atorvastatin Tablets if you have:
- had a previous stroke caused by bleeding
- kidney problems
- an under-active thyroid gland (hypothyroidism)
- (or have had) repeated or unexplained muscle aches or pains or a family history of muscle problems
- had previous muscle problems during treatment with other cholesterol-lowering medicines (i.e. other statins or "librate" medicines)
- had liver disease

also take special care with Atorvastatin Tablets and if you:
- regularly drink a large amount of alcohol
- are older than 70 years

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

The above are reasons why Atorvastatin Tablets may not be suitable for you. If any of the above reasons apply to you, your doctor will need to carry out a blood test before and possibly during your treatment with Atorvastatin Tablets especially to predict your risk of muscle related side effects. The risk of muscle related side effects 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 Tablets or their effect may be changed by Atorvastatin Tablets. 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:
- 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 lower cholesterol e.g. gemfibrozil, other fibrates, colestevel
- Medicines used for angina or high blood pressure known as "calcium channel blockers" e.g. amlopidine, diltiazem
- Medicines to regulate your heart rhythm e.g. digoxin, verapamil, amiodarone
- Medicines used in the treatment of HIV e.g. ritonavir, lopinavir, stavudine, tenofovir, darunavir
- Other medicines known to interact with Atorvastatin Tablets include ezetimibe (lowers cholesterol), warfarin (reduces blood clotting), oral contraceptives, aspirin (for headaches), cimetidine (for heartburn and peptic ulcers), phenazone (a painkiller) and antacids (indigestion products containing aluminium or magnesium)
- Medicines obtained without a prescription: see St John's Wort

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

Taking Atorvastatin Tablets with food and drink
See Section 3 for instructions on how to take Atorvastatin 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 Tablets.

Alcohol
Avoid drinking too much alcohol while taking this medicine.

Pregnancy and Breast-feeding
Do not take Atorvastatin Tablets if you are pregnant, or if you are trying to become pregnant. Do not take Atorvastatin Tablets if you are able to become pregnant unless you use reliable contraception measures.
Do not take Atorvastatin Tablets if you are breastfeeding. The safety of Atorvastatin Tablets during pregnancy and breastfeeding has not yet 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 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 TABLETS
Before starting treatment, your doctor will advise you on a low-cholesterol diet you should continue this diet whilst taking Atorvastatin Tablets.

The usual starting dose of Atorvastatin 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 dose at intervals of 4 weeks or more. The maximum dose of Atorvastatin Tablets is 80 mg once daily for adults and 20 mg once daily for children.

Atorvastatin Tablets should be swallowed whole with a drink of water, this 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 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 Tablets is determined by your doctor. Please ask your doctor if you think that the effect of Atorvastatin Tablets is too strong or too weak.

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

If you forget to take Atorvastatin 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 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 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.

Uncommon: affects 1 to 10 users in 1000:
• inflammation and pain in the upper airways, nose bleed
• allergic reactions
• increased blood sugar (if you have diabetes continue careful monitoring of your blood sugar levels)
• headache
• nausea, constipation, wind, indigestion, diarrhoea
• joint pain, muscle pain and back pain
• changes in blood test results that report on your muscles and liver

Uncommon: affects 1 to 10 users in 1000:
• loss of appetite, vomiting, belching, abdominal pain
• loss of concentration, disturbed sleep
• dizziness, ringing in the ears (tinnitus)
• numbness or tingling in the fingers and toes, reductions of sensation to pain or touch
• change in sense of taste
• loss of memory
• visual disturbance
• liver problems
• skin rash, itching, hives, hair loss
• neck pain, chest pain

• fatigue, feeling unwell, weakness
• fluid retention causing swelling of the extremities
• headache
• a urine test that gives a positive result for the presence of white blood cells

Rare: affects 1 to 10 users in 10,000:
• jaundice (yellowing of skin)
• sore muscle tendons that may rupture

Very rare: affects less than 1 user in 10,000:
• hearing loss
• increase in breast tissue in men

Possible side effects reported with some statins (medicines of the same type):
• sexual difficulties
• depression
• breathing problems including persistent cough and/or hoarseness 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 TABLETS
Keep out of the reach and sight of children.
Store in the original package in order to protect from moisture. This medicine does not require any special temperature storage conditions.

Do not use Atorvastatin Tablets after the expiry date which is stated on the carton label and blister foil 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 Tablets contains
The active substance is atorvastatin.
Each film-coated tablet contains 10 mg of atorvastatin as Atorvastatin calcium hemi-hydrate.
Each film-coated tablet contains 20 mg of atorvastatin as Atorvastatin calcium hemi-hydrate.
Each film-coated tablet contains 40 mg of atorvastatin as Atorvastatin calcium hemi-hydrate.

The other ingredients of Atorvastatin Tablets are: Starch pregelatized, lactose monohydrate, crospovidone, hydroxypropyl cellulose, silica colloidal anhydrous, magnesium stearate.

The film-coating of Atorvastatin Tablets contains lactose monohydrate, hypromellose, titanium dioxide (E-171), macrogol 4000 and carnauba wax.

What Atorvastatin Tablets looks like and contents of the pack
Atorvastatin 10 mg and 20 mg film-coated tablets are white with a round shape.
Atorvastatin 40 mg film-coated tablets are white with a capsule shape.

Atorvastatin Tablets are available in blister packs containing 28 film-coated tablets.

Marketing Authorisation Holder and Manufacturer
Dexcel-Pharma Ltd, 7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PS, UK

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

Ireland, UK
Atorvastatin 10 mg/20 mg/40 mg film-coated tablets
France, Germany
Atorvastatin Dexcel 10 mg/20 mg/40 mg film-coated tablets

This leaflet was last approved in 08/2011.
Module 4

Labelling

PL 14017/0198:

Label

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ATORVASTATIN 40mg FILM-COATED TABLETS

28 Tablets

Atorvastatin

MARKETING AUTHORISATION HOLDER:
DEXCEL PHARMA LTD.
7 Sopwith Way, Drayton Fields, Daventry,
Northamptonshire NN11 8PB, UK.

Each tablet contains: 40 mg atorvastatin as Atorvastatin calcium hemi-hydrate.
Also contains lactose, see leaflet for further information.
Keep out of the reach and sight of children.
Dosage: For oral use, as directed by your doctor. Read the package leaflet before use.
Store in the original package in order to protect from moisture.
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets in the treatment of hypercholesterolaemia could be approved.

EXECUTIVE SUMMARY

Problem statement
These Decentralised applications were submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claimed that the proposed products are generic versions of the products Lipitor 10mg, 20mg and 40mg film coated tablets, marketed by Pfizer Limited (PL 39933/0001-0003). Lipitor was authorised in the UK on 7 November 1996 by Parke Davis & Co. Ltd. As the reference products have been authorised in the EU for more than 10 years, the legal basis of these applications is acceptable.

With the UK as the Reference Member State in these Decentralised Procedures, Dexcel®-Pharma Ltd. applied for Marketing Authorisations for Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets in Germany, France and Ireland.

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

Atorvastatin is rapidly absorbed from the gastrointestinal tract. It has low absolute bioavailability of about 12%, due to presystemic clearance in the gastrointestinal mucosa and/or first-pass metabolism in the liver, its primary site of action. Atorvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4 to a number of active metabolites. It is 98% bound to plasma proteins. The mean plasma elimination half-life of atorvastatin is about 14 hours, although the half-life of inhibitory activity for HMG-CoA reductase is about 20 to 30 hours, due to the contribution of the active metabolites. Atorvastatin is excreted as metabolites, primarily in the bile.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossiers regarding the quality, non-clinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles
GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly 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.

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

GLP
No new non-clinical studies were submitted in support of these applications, and none are needed for applications of this type.

GCP
Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

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

(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1Hpyrrol-1-yl]-3,5-dihydroxyheptanoic acid, calcium salt (2:1)

CAS registry number: 134523-03-8
Molecular formula: C₆₆H₆₈CaF₂N₄O₁₀
Relative molecular mass: 1155.36
Structure:

General Properties:
White to off white crystalline powder. Freely soluble in methanol, soluble in dimethyl sulfoxide, slightly soluble in ethanol and very slightly soluble in water in the range of pH from 6 to 10.

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

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of analysis for all working standards have been provided. Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with foodstuffs.

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

Drug product

Description and composition
Atorvastatin 10 mg and 20 mg film-coated tablets are white and round; Atorvastatin 40 mg film-coated tablets are white and capsule-shaped. The cores of these tablets contain the excipients pregelatinised starch, lactose monohydrate, crospovidone, hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate. The tablet coating contains lactose monohydrate, hypromellose, titanium dioxide (E-171) and macrogol 4000. Carnauba wax is used to polish the tablets.

The excipients used in the tablet comply with current Ph. Eur. monograph requirements and are, therefore, acceptable. Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

Pharmaceutical development
The objective of the development programme was to develop a formulation similar to the innovator products, Lipitor 10mg, 20mg and 40mg film coated tablets. A satisfactory account of the pharmaceutical development has been provided.
Manufacturing process
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

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

Container-closure system
The tablets are available in blister packs containing 28 film-coated tablets. The tablets are packed in blisters made of PVC/OPA-coated aluminium strips sealed with aluminium foil.

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

Stability of the product
Stability studies were performed in accordance with current guidelines on the finished products in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for these products when they are stored in the original package in order to protect from moisture.

Product literature
The SmPCs, PILs and labels are pharmaceutically acceptable.

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

Marketing Authorisation Application (MAA) forms
The MAA forms are pharmaceutically satisfactory.

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

Quality conclusion
There are no objections to the approval of Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets from a quality point of view.
Non-clinical aspects

Non-clinical overview
The pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well known and have been adequately reviewed in the non-clinical overview. The absence of new non-clinical studies is acceptable for these applications.

Expert report
The non-clinical overview has been written by an appropriately qualified person. The report refers to 10 publications up to the year 2010. In view of the fact that the pharmaco-toxicological properties of atorvastatin are well known, the overview is acceptable.

Environmental risk assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all atorvastatin containing products, which in turn is unlikely to increase exposure of the environment to these drug substances.

Product literature
The product literature is acceptable from a non-clinical point of view.

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

Clinical aspects

Bioequivalence study
A randomized, open label, two-sequence, two-treatment, two-period, crossover, single dose, bioequivalence study of Atorvastatin 40 mg Tablets and Lipitor 40 mg Tablets in normal, healthy, adult, male and female human subjects under fasting condition was conducted.

Study design
80 subjects (75 male and 5 female) aged 18 to 55 years, with a body mass index 18–26 kg/m$^2$ were enrolled.

One subject was withdrawn in period 1 because of an adverse event: 5 subjects did not attend for period 2 of the study and 3 subjects were withdrawn at the start of period 2 because of a violation of the protocol (tested positive for drugs of abuse). 71 subjects were analysed and included in the statistical analysis.

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

Protocol
Subjects were admitted to the study facility and fasted overnight for about 10 hours: subjects were given the study medication with water and then remained in the study facility for 24 hours. Blood was collected prior to administration of drug and then at intervals up to 48 hours after drug administration. A washout period of 13 days was used between testing.

The schedule of blood collection is adequate for $\text{AUC}_{t>80\%}$ of $\text{AUC}_{\text{inf}}$. The sampling frequency around $T_{\text{max}}$ was adequate for accurate $C_{\text{max}}$ estimation. The washout period of 13 days is adequate to avoid carry-over.

Safety
Safety was evaluated by physical examination, laboratory testing and by monitoring vital signs and for adverse events during the study periods.

All adverse events were considered to be mild or moderate and resolved: only two of the adverse events (headache) were considered to be related to study medication. The safety issues reported were too few in number in the test and reference product arms of the study to be of any meaning.

Bio-analytical results
Method of data analysis: $\text{AUC}$ and $C_{\text{max}}$ were calculated by statistical analysis of a parametric ANOVA model of log-transformed data. $T_{\text{max}}$ was calculated by a non-parametric method.

Results for main pharmacokinetic parameters of atorvastatin:

<table>
<thead>
<tr>
<th>Measures</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>$\text{AUC}_{0-t}$ (ng*hr/mL)</th>
<th>$\text{AUC}_{0-\text{inf}}$ (ng*hr/mL)</th>
<th>$T_{\text{max}}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Product- A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>71</td>
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<tr>
<td>Mean</td>
<td>45.32</td>
<td>158.17</td>
<td>162.48</td>
<td>1.46</td>
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<tr>
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<td>67.39</td>
<td>68.11</td>
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<tr>
<td>CV (%)</td>
<td>58.88</td>
<td>42.61</td>
<td>41.92</td>
<td>75.91</td>
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<tr>
<td><strong>Reference Product- B</strong></td>
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<tr>
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<tr>
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<td>156.86</td>
<td>161.92</td>
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<tr>
<td>SD</td>
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<td>CV (%)</td>
<td>54.03</td>
<td>40.72</td>
<td>40.26</td>
<td>75.46</td>
</tr>
</tbody>
</table>

Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:
The 90% confidence intervals for test/reference ratio lie within the acceptance criteria of 80–125. This is acceptable. The applicant has also returned results for o-hydroxyatorvastatin within the 80–125 limits.

The mean plasma concentration – time curve for atorvastatin is shown below:

The inter-individual variations displayed are consistent with known data. The plasma concentration – time curves are acceptable.

**Pharmacokinetic conclusion**

The applicant has submitted results that are consistent with bioequivalence between the test and reference products.

As Atorvastatin 10 mg, 20 mg and 40 mg film-coated tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr), the results and conclusions of the bioequivalence study on the 40 mg strength tablets can be extrapolated to the 10 and 20mg strength tablets.
Pharmacodynamic studies
No new data has been submitted and none is required. This is acceptable for generic applications.

Additional data
The dissolution profiles of the proposed product and the reference product used in bioequivalence study have been shown to be comparable.

Clinical efficacy
No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of atorvastatin.
Pharmacovigilance system
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for these applications.

Expert report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

Product literature
All product literature (SmPCs, PIL and labelling) is medically satisfactory.

Clinical conclusion
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Atorvastatin 10 mg, 20 mg and 40 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 and none are required for applications of this type.

EFFICACY
The use of atorvastatin in the treatment of hypercholesterolaemia is well established. Bioequivalence has been demonstrated between the applicant’s products and the reference products. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SmPCs and PILs are satisfactory and consistent with those of the reference products. Satisfactory labelling has also been submitted.

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 is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be acceptable. Marketing Authorisations should be granted.