# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific discussion</td>
<td>3</td>
</tr>
<tr>
<td>Steps taken for assessment</td>
<td>40</td>
</tr>
<tr>
<td>Steps taken after authorisation – summary</td>
<td>41</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>42</td>
</tr>
<tr>
<td>Product Information Leaflet</td>
<td>98</td>
</tr>
<tr>
<td>Labelling</td>
<td>103</td>
</tr>
</tbody>
</table>
LIPITOR 5MG, 10MG, 20MG AND 40MG CHEWABLE TABLETS
PL 16051/0006-9

LAY SUMMARY

On 3rd November 2010, the MHRA granted Pfizer Ireland Pharmaceuticals Limited Marketing Authorisations (licences) for Lipitor 5mg, 10mg, 20mg and 40mg chewable tablets.

Lipitor chewable tablets contain atorvastatin. Atorvastatin belong to a group of medicines known as statins.

These tablets act by lowering fats (also called cholesterol) in the blood when a low fat diet and lifestyle changes on their own have failed.

Cholesterol is a naturally occurring substance in the body necessary for normal growth. However, if there is too much cholesterol in your blood it can be deposited in the walls of blood vessels leading to the narrowing of these vessels, which may eventually, become blocked. This is one of the most common causes of heart disease. It is accepted that raised cholesterol levels increase the risk of heart disease.

For diabetics or people with at least one other risk factor for cardiovascular disease, this medicine can reduce the risk of you having a heart attack or stroke.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lipitor 5mg, 10mg, 20mg and 40mg chewable tablets outweigh the risks; hence Marketing Authorisations have been granted.
LIPITOR 5MG, 10MG, 20MG AND 40MG CHEWABLE TABLETS
PL 16051/0006-9

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 4
Pharmaceutical assessment Page 6
Pre-clinical assessment Page 9
Clinical assessment (including statistical assessment) Page 10
Overall conclusions and risk benefit assessment Page 39
INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Lipitor 5mg, 10mg, 20mg and 40mg chewable tablets (PL 16051/0006-9) to Pfizer Ireland Pharmaceuticals Limited on 3rd November 2010. These prescription only medicines are indicated for:

i) Hypercholesterolaemia

- reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with prima hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

- Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

- Lipitor is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in adults with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

ii) Primary prevention in type II diabetes

- reducing the risk of cardiovascular events in diabetic patients with at least one additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol is raised.

These applications for Lipitor 5mg, 10mg, 20mg and 40mg chewable tablets (PL 16051/0006-9) are submitted according to Article 8.3 of Directive 2001/83/EC.

These applications are for a line extension to existing Marketing Authorisations for Lipitor 10mg, 20mg, 40mg and 80mg tablets (PL 16051/0001-3, 5). Lipitor 80mg Tablets were first authorised on 15th August 2000 to Pfizer Ireland Pharmaceuticals Limited. Lipitor 10mg, 20mg and 40mg were first authorised on 7th November 1996.

These applications are for a line extension including a new strength (5mg) and a new pharmaceutical form (chewable tablets). These applications have been considered under Article 29 of Regulation (EC) No 1901/2006. The procedure numbers are as follows:

- EMEA/H/A-29 PAD/1253 (new paediatric appropriate pharmaceutical form)
- EMEA/H/A-29 PAD/1254 (new strength)

The decision of the European Commission was published on 1st July 2010.

Link to list of referrals for human medicinal products.

The data considered in the Article 29 procedure form the basis of this report.

Atorvastatin calcium is a synthetic 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor. This enzyme is involved in cholesterol biosynthesis by catalyzing the conversion reaction of HMG-CoA to mevalonic acid. The function of lowering the amount of cholesterol leads to the result in clearing the low-density lipoprotein (LDL) receptor upregulation, and increased hepatic clearance of plasma LDL. The calcium
salt of atorvastatin is used in the treatment of primary hypercholesterolemia and dyslipidemia.

It is considered that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

The Marketing Authorisation Holder has provided a satisfactory Risk Management Plan (RMP) including routine and additional risk minimisation measures.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Lipitor 5mg, 10mg, 20mg and 40mg chewable tablets outweigh the risks; hence these Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Atorvastatin calcium
INN: Atorvastatin calcium
Chemical name: Calcium (βR,δR)-2-(p-fluorophenyl)-β,δ-dihydroxy-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)pyrrole-1-heptanoic acid (1:2) trihydrate.

Structural formula:

Molecular formula: C\textsubscript{66}H\textsubscript{68}CaF\textsubscript{2}N\textsubscript{4}O\textsubscript{10}
Molecular weight: 1155.36
Appearance: White to off-white crystalline powder.
Solubility: Practically insoluble in aqueous solutions of pH 4 and below. Slightly soluble in water, ethanol and in pH 7.4 phosphate buffer. Sparingly soluble in acetonitrile and freely soluble in methanol.

Atorvastatin calcium complies with in-house specifications.

The Marketing Authorisation Holder has confirmed that no further changes have been made to the drug substance and that it is identical to that which was previously assessed and approved for Lipitor 10mg, 20mg, 40mg and 80mg tablets (PL 16051/0001-3, 5).

DRUG PRODUCT
Other ingredients
Other ingredients in the tablet granules consist of pharmaceutical excipients calcium carbonate, microcrystalline cellulose, croscarmellose sodium, polysorbate 80, magnesium stearate, hydroxypropyl cellulose, amyllum pregelificatum, mannitol (E421), aspartame (E951), sucralose (E955) and grape flavour.

With the exception of grape flavour, all the ingredients in the tablet granules and the capsule shell comply with their relevant European Pharmacopoeia monographs. Grape flavour complies with in-house specifications.

None of the excipients used contain material of animal or human origin, which is supported by a statement from the Quality Expert. The magnesium stearate is of vegetable origin.
Product development
The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Satisfactory dissolution data have been provided.

Manufacture
A description of the manufacturing method has been provided.

In-process controls are satisfactory based on manufacturing process development data and batch data provided to date. The applicant has committed to perform process validation on the future commercial-scale batches.

Finished product specification
The finished product specifications proposed for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.

Container-Closure System
The product is packaged in blisters that consist of a forming foil made of polyamide, aluminium foil and polyvinyl chloride (PVC) and a backing made of aluminium foil, vinyl and an acryl heat-seal coating.

The product is available in packs of 30 chewable tablets.

Specifications and Certificates of Analysis for the packaging types used have been provided. All primary product packaging complies with the European Pharmacopoeia monograph.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set, with no storage conditions. This is satisfactory.
ADMINISTRATIVE

Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)
The proposed Summary of Product Characteristics is pharmaceutically acceptable and is in line with the Commission Decision following an article 29 application under regulation (EC) No 1901/2006 EMA procedure number EMEA/H/A-PAD 29/1254.

Labelling
The labelling used is appropriate and in compliance with the QRD template and article 54 of the EC 2001/83 as amended.
In-line with current legislation, the applicant has also included the name of the product in Braille on the packaging and has included sufficient space for a standard UK pharmacy dispensing label.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.
User testing for the PIL has not been done, the PIL is based on current Mutual Recognition (MR)/national leaflets for the licensed products Lipitor 10mg, 20mg, 40mg and 80 mg tablets (PL 16051/0001-3, 5). The revisions to the package leaflet are not considered to significantly change the reliability of the leaflet; therefore the submission of a user consultation is not deemed necessary.

MAA Form
These are pharmaceutically satisfactory.

Conclusion
The active substances manufacture and control is essentially the same as that reviewed for the already authorised strength.
It is recommended that Marketing Authorisations are granted for these applications.
PRE-CLINICAL ASSESSMENT

No new pre-clinical data have been supplied with this application. The extension of indications was supported by clinical data.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
The following clinical assessment is taken from the assessment reports EMEA/H/A-29 PAD/1253 and EMEA/H/A-29 PAD/1254. Please note that Lipitor tablets may be referred to as Sortis tablets which is the brand name used in some other European Member States for the same product.

The paediatric development program for the new indication comprises the following studies:

- Two completed bioequivalence studies in healthy volunteers investigating the chewable tablet formulation
- Four completed paediatric studies:
  - one pivotal pharmacokinetic/pharmacodynamic (PK/PD) study (Study A2581172), conducted in accordance with the agreed Paediatric Investigation Plan (PIP),
  - three supportive studies (Study 981-147, Study 981-336, and Study 981-080)
- An on-going follow-up study (Study A2581173) to assess the efficacy and safety and tolerability in the long-term, conducted in accordance with the agreed PIP.

### Table 1. Studies in paediatric patients providing efficacy data

<table>
<thead>
<tr>
<th>Study Identification</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Number of Subjects*</th>
<th>Study Arms</th>
<th>Duration of Follow-up</th>
<th>Efficacy Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>A2581172</td>
<td>Open-label, multicentre</td>
<td>Children and adolescents with FH (+/-) (12 yrs to &lt;18 yrs)</td>
<td>39 (Col A: 15 subjects; Col B: 24 subjects)</td>
<td>Atorvastatin 5 mg/day OR 10 mg/day</td>
<td>5 weeks</td>
<td>LDL-C, TC, TG, HDL-C, LDL-C, HDL-C, VLDL-C, Apo A-I, Apo B, FMD</td>
</tr>
<tr>
<td>981-147</td>
<td>Double-blind, placebo controlled, multicentre</td>
<td>Children and adolescents (10 to 17 yrs) with FH or severe HC</td>
<td>187</td>
<td>Atorvastatin 10 mg/day OR Placebo</td>
<td>26 weeks in double-blind phase; 26 weeks open-label extension</td>
<td>LDL-C, TC, TG, HDL-C, Apo A-I, Apo B</td>
</tr>
<tr>
<td>981-336</td>
<td>Open-label, parallel group, multicentre</td>
<td>Children and adolescents (10 to 18 yrs) with FH and HC</td>
<td>58</td>
<td>Atorvastatin 10 mg/day OR Colestipol 2 g/day</td>
<td>52 weeks</td>
<td>LDL-C, TC, TG, HDL-C, VLDL-C, TC, HDL-C, LDL-C, HDL-C</td>
</tr>
<tr>
<td>981-080</td>
<td>Open-label, comparable centre, multicentre</td>
<td>HoFH or SBC</td>
<td>335 (2 to 73 years of age; &lt;18 yrs of age)</td>
<td>Atorvastatin 2.5 mg/day to 10 mg/day</td>
<td>&lt;2 weeks to &gt;2 years</td>
<td>LDL-C, TC, TG, HDL-C</td>
</tr>
</tbody>
</table>

*Number of subjects randomized. 
1.1.1 GCP aspects

The Marketing Authorisation Holder has conducted two bioequivalence studies to support this line extension of chewable tablets for paediatric use:

Bioequivalence between the chewable tablets and the film-coated tablets has been shown by means of two bioequivalence studies (A2581174 and A2581175).
1) An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a Paediatric Appropriate Formulation to a 10mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects, and

2) An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a New 80mg (2x40mg) Paediatric Appropriate Formulation to an 80mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects.

The MAH has declared that these studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed.

1.1.2 Pharmacokinetics

According to the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, a bioequivalence study investigating only one strength may be acceptable if a new application concerns several strengths of the active substance. However the choice of the strength used should be justified on analytical, pharmacokinetic and safety grounds. The two extremes of the strength range have been investigated due to the non-linear kinetics of atorvastatin, and it was concluded that the evidence of bioequivalence demonstrated for the 5mg and 40mg chewable tablets can be extrapolated to the 10mg and 20mg strengths.

Bioequivalence study for the 5 mg strength (study A2581174): An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study Comparing a Paediatric Appropriate Formulation to a 10mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects

Objective

Primary objective:
- To determine whether two 5mg (10mg) of a new atorvastatin calcium chewable tablets were bioequivalent to one 10mg commercial atorvastatin calcium tablet formulation.

Secondary objective:
- Assess safety and tolerability of atorvastatin in different formulations in healthy volunteers.

Study design

This was an open label, randomized, single-dose, 2-way crossover study in 74 healthy subjects. Subjects attended a screening visit and participated in 2 treatment periods each of 5 days. The 2 treatment periods were separated by a washout period of at least 14 days and were preceded by an 8-hour overnight fast. Each subject received one 10mg tablet of a commercial tablet formulation or two 5mg (10mg) tablets of the chewable tablet formulation according to a randomization schedule. During treatment period 2, subjects received the study treatment not administered in treatment period 1.

During both treatment periods, blood samples were collected before dosing on Day 1, and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after dosing with either the new or commercial atorvastatin tablets. Plasma samples were analyzed for concentrations of
atorvastatin and its active hydroxyacid metabolites (ortho-hydroxyatorvastatin and para-
hydroxyatorvastatin) using a validated, sensitive, and specific liquid chromatography
 tandem mass spectrometric (LC/MS/MS) method. The following pharmacokinetic (PK)
 parameters were calculated for atorvastatin acid, ortho-hydroxyatorvastatin, and
 para-hydroxyatorvastatin: Area under the plasma concentration-time profile from time zero
to the time of the last quantifiable concentration (AUClast); area under the plasma
concentration-time profile from time zero extrapolated to infinite time (AUCinf); maximum
plasma concentration (Cmax), time for Cmax (Tmax), and the terminal elimination half-life
(t1/2).

Subject disposition
Seventy-four (74) subjects were planned to be enrolled in this study. Seventy-six (76)
subjects were assigned to study treatment. Of the 76 subjects who were assigned to
treatment, 2 were replacement subjects for 2 of the 4 subjects who discontinued from the
study. Four subjects did not complete the study. In one case the subject discontinued for a
reason not related to study treatment (subject was withdrawn because of a positive urine
drug test) and 3 subjects discontinued because the subject was no longer willing to
participate in study.

Table 2. Subject disposition

<table>
<thead>
<tr>
<th>Number (%) of subjects</th>
<th>Two 5mg (10 mg) Tablets of New Atorvastatin</th>
<th>One 10mg Tablet of Commercial Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assigned to study treatment N = 76</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treated</td>
<td>75</td>
<td>76</td>
</tr>
<tr>
<td>Completed</td>
<td>75 (100.0)</td>
<td>72 (94.7)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>0</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Not related to study treatment</td>
<td>0</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>

N = number of subjects randomized; n = number of subjects in the indicated category.

Pharmacokinetic Variables
The PK parameter analysis set, which was defined as all subjects enrolled and treated who
had at least 1 of the PK parameters of primary interest in at least 1 treatment period, was
used for PK parameter analyses. Primary study endpoints were AUClast, AUCinf (if data
permitted), and Cmax, from plasma atorvastatin concentration data. Secondary endpoints
included Tmax and t1/2 (if data permitted) of atorvastatin; AUClast, AUCinf, Cmax, Tmax, and t1/2
(if data permitted) of ortho-hydroxyatorvastatin and para-hydroxyatorvastatin. AUClast was
calculated by the linear/Log trapezoidal method. AUCinf was calculated as AUClast +
(Clast*/kel), where Clast was the predicted plasma concentration at the last quantifiable time
point estimated from the log-linear regression analysis. Cmax was observed directly from
data.

Statistical methods
Natural log transformed AUCinf (if data permitted), AUClast, and Cmax of atorvastatin were
analyzed using a mixed effects model with sequence, period, and treatment as fixed effects
and subject-within-sequence as a random effect. Estimates of the adjusted mean differences
of the Test (new atorvastatin [two 5mg] tablets) to Reference (commercial atorvastatin [one
10mg] tablet) and corresponding 90% confidence intervals (CIs) were obtained from the
model. The adjusted mean differences and 90% CIs for the differences were exponentiated
to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Residuals from the model were examined for normality and the presence of outliers via visual inspection of plots of residuals versus predicted values and normal probability plots of residuals.

Bioequivalence of the Test to Reference was concluded if the 90% CIs for the ratios (Test/Reference) of adjusted geometric means for both AUC_{inf} (if data permitted, otherwise AUC_{last}) and C_{max} of atorvastatin fell entirely within (80%, 125%). The statistical model is considered adequate.

**Results**

After dosing with 10mg atorvastatin, the pharmacokinetics of both atorvastatin and its ortho-hydroxyatorvastatin metabolite were similar for the new atorvastatin (two 5mg) and the commercial atorvastatin (one 10mg) tablet formulations (Table 3).

**Table 3. Descriptive Summary of Plasma Atorvastatin and Ortho-Hydroxyatorvastatin Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>PK Parameter (units)</th>
<th>Two (5 mg) Tablets of New Atorvastatin (N = 75)</th>
<th>One 10 mg Tablet of Commercial Atorvastatin (N = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{inf} (ng.h/mL)</td>
<td>Atorvastatin 22.82 (40)</td>
<td>Atorvastatin 22.14 (41)</td>
</tr>
<tr>
<td></td>
<td>Ortho-Hydroxyatorvastatin 24.45 (37)</td>
<td>Ortho-Hydroxyatorvastatin 24.40 (37)</td>
</tr>
<tr>
<td>AUC_{last} (ng.h/mL)</td>
<td>20.51 (43)</td>
<td>19.80 (43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.84 (41)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>3.799 (52)</td>
<td>3.508 (42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.482 (52)</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>0.50 (0.25 – 1.50)</td>
<td>0.50 (0.40 – 4.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.00 (0.50 – 9.02)</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>10.21 (2.9300)</td>
<td>10.82 (2.3281)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.34 (2.9983)</td>
</tr>
</tbody>
</table>

AUC_{inf} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration; AUC_{last} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max} = maximum plasma concentration; N = number of subjects evaluable for pharmacokinetics; PK = pharmacokinetic; T_{max} = time for C_{max}; t_{1/2} = terminal elimination half-life.

a Geometric means (coefficient of variation %) for AUC_{inf}, AUC_{last}, and C_{max}; median (range) for T_{max}; and arithmetic mean (standard deviation) for t_{1/2}.

b Only 75 subjects contributed to these summary statistics.

The bioequivalence criteria were met for both C_{max} and AUC_{inf} of atorvastatin (Table 3). The 90% CIs for the ratio of the adjusted geometric means for both AUC_{inf} and C_{max} of atorvastatin lay entirely within the acceptance range for bioequivalence, ie, (80%, 125%).

For both the new and commercial atorvastatin tablet formulations, the plasma concentrations of para-hydroxyatorvastatin were below the limit of quantitation for most...
samples collected and the PK parameters could not be accurately calculated for the majority of subjects.

Safety data
There were no deaths, serious adverse events (AE), discontinuations due to AEs, or dose reductions due to AEs in this study. A similar percentage of subjects reported all causality AEs after dosing with the new atorvastatin (two 5mg) tablets (5 [6.7%] subjects) and after dosing with the commercial atorvastatin (one 10mg) tablet (4 [5.3%] subjects). A higher percentage of subjects reported treatment-related AEs after dosing with the new atorvastatin (two 5mg) tablets (4 [5.3%] subjects) than after dosing with the commercial atorvastatin (one 10mg) tablet (1 [1.3%] subject).
The safety profile of both products seems to be comparable.

Bioequivalence study for the 80mg strength (study A2581175): An Open Label, Randomized, Single Dose, Two-Way Crossover Bioequivalence Study comparing a new 80mg (2x40mg) Paediatric Appropriate Formulation to an 80mg Commercial Atorvastatin Calcium Tablet Formulation in Healthy Subjects

Objectives:
Primary objective:
• Determine whether 80mg (2x40mg) of the new formulation atorvastatin calcium chewable tablets were bioequivalent to 80mg of the commercial atorvastatin calcium tablet formulation.

Secondary objective:
• Assess safety and tolerability of atorvastatin in different formulations in healthy volunteers.

Study design
This was an open label, randomized, single-dose, 2-way crossover study in 74 healthy subjects. Subjects attended a screening visit and participated in 2 treatment periods each of 5 days. The 2 treatment periods were separated by a washout period of at least 14 days and were preceded by an 8-hour overnight fast. Each subject received one 80mg tablet of the commercial atorvastatin tablet formulation or two 40mg (80mg) tablets of the new atorvastatin calcium chewable tablet formulation according to a randomization schedule. During Treatment Period 2, subjects received the study treatment not administered in Treatment Period 1.

During both treatment periods, blood samples were collected before dosing on Day 1, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours after dosing with either the new or commercial atorvastatin tablets. Plasma samples were analyzed for concentrations of atorvastatin and its active hydroxyacid metabolites (ortho-hydroxyatorvastatin and para-hydroxyatorvastatin) using a validated, sensitive and specific liquid chromatography tandem mass spectrometric (LC/MS/MS) method. The following pharmacokinetic (PK) parameters were calculated for atorvastatin acid, ortho-hydroxyatorvastatin, and para-hydroxyatorvastatin: Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUC_{last}); area under the plasma concentration-time profile from time zero extrapolated to infinite time ([AUC_{int}], if data permitted); maximum plasma concentration (C_{max}), time for C_{max} (T_{max}), and the terminal elimination half-life ([t_{1/2}], if data permitted).
Subject disposition
Seventy-four (74) subjects were planned to be enrolled in this study. Seventy-six (76) subjects were assigned to study treatment: 73 subjects received the new atorvastatin (two 40mg) tablets and 75 subjects received the commercial atorvastatin (one 80mg) tablet. Seventy-two (72 [98.6%]) subjects completed treatment with the new atorvastatin (two 40mg) tablets and 70 (93.3%) subjects completed treatment with the commercial atorvastatin (one 80mg) tablet. One (1.4%) subject after dosing with the new atorvastatin (two 40mg) tablets and 5 (6.7%) subjects after dosing with the commercial atorvastatin (one 80mg) tablet were discontinued from the study. Two subjects were discontinued from the study after dosing with the commercial atorvastatin (one 80mg) tablet because of treatment-related AEs, and 3 subjects were discontinued from the study after dosing with the commercial (one 80mg) tablet because of other reasons not related to the study treatment.

Pharmacokinetic Variables
The PK parameter analysis set, which was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest in at least 1 treatment period, was used for PK parameter analyses. Primary study endpoints were $\text{AUC}_{\text{last}}$, $\text{AUC}_{\text{inf}}$ (if data permitted), and $\text{C}_{\text{max}}$ from plasma atorvastatin concentration data. Secondary endpoints included $\text{T}_{\text{max}}$ and $t_{1/2}$ (if data permitted) of atorvastatin; $\text{AUC}_{\text{last}}$, $\text{AUC}_{\text{inf}}$, $\text{C}_{\text{max}}$, $\text{T}_{\text{max}}$, and $t_{1/2}$ (if data permitted) of ortho-hydroxyatorvastatin and para-hydroxyatorvastatin. $\text{AUC}_{\text{last}}$ was calculated by the linear/Log trapezoidal method. $\text{AUC}_{\text{inf}}$ was calculated as $\text{AUC}_{\text{last}} + (\text{C}_{\text{last}}*/\text{kel})$, where $\text{C}_{\text{last}}$ was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. $\text{C}_{\text{max}}$ was observed directly from data.

Statistical methods
Bioequivalence of PK parameters of atorvastatin was to be determined by constructing 90% CIs around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model was implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

Natural log transformed $\text{AUC}_{\text{inf}}$ (if data permitted), $\text{AUC}_{\text{last}}$, and $\text{C}_{\text{max}}$ of atorvastatin were analyzed using a mixed effects model with sequence, period, and treatment as fixed effects and subject-within-sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. Residuals from the model were examined for normality and the presence of outliers via visual inspection of plots of residuals versus predicted values and normal probability plots of residuals. Bioequivalence of the Test to Reference was demonstrated if the estimated 90% CIs for the ratios (Test/Reference) of adjusted geometric means for both $\text{AUC}_{\text{inf}}$ (if data permitted, otherwise $\text{AUC}_{\text{last}}$) and $\text{C}_{\text{max}}$ of atorvastatin fell entirely within (80%, 125%). The statistical model is considered adequate.
Results
After dosing with 80mg atorvastatin, the pharmacokinetics of atorvastatin were similar for the new atorvastatin (two 40mg) and the commercial atorvastatin (one 80mg) tablet formulations (Table 4).

Table 4. Descriptive Summary of Plasma Atorvastatin Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>PK Parameter³ (units)</th>
<th>Two 40 mg (80 mg) Tablets of New Atorvastatin (N=73)</th>
<th>One 80 mg Tablet of Commercial Atorvastatin (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{\text{inf}} ) (ng h/mL)</td>
<td>131.9 (41)</td>
<td>124.5 (40)</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{max}} ) (ng h/mL)</td>
<td>128.2 (43)</td>
<td>121.3 (41)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>29.23 (49)</td>
<td>28.94 (50)</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>0.50 (0.25 - 6.02)</td>
<td>0.50 (0.50 - 6.00)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>6.059 (2.3267)</td>
<td>6.479 (2.0262)</td>
</tr>
</tbody>
</table>

\( \text{AUC}_{\text{inf}} = \text{area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration} \)
\( \text{AUC}_{\text{max}} = \text{area under the plasma concentration-time profile from time zero extrapolated to infinite time} \)
\( C_{\text{max}} = \text{maximum plasma concentration} \)
\( T_{\text{max}} = \text{time for } C_{\text{max}} \)
\( t_{1/2} = \text{terminal elimination half-life} \)
\( N = \text{number of subjects evaluable for pharmacokinetics} \)

³ Geometric mean (coefficient of variation %) for \( \text{AUC}_{\text{inf}}, \text{AUC}_{\text{max}}, \text{and } C_{\text{max}} \); median (range) for \( T_{\text{max}} \); and arithmetic mean (standard deviation) for \( t_{1/2} \).

The bioequivalence criteria were met for both \( C_{\text{max}} \) and \( \text{AUC}_{\text{inf}} \) of atorvastatin (Table 5). The 90% CIs for the ratio of the adjusted geometric means for both \( \text{AUC}_{\text{inf}} \) and \( C_{\text{max}} \) of atorvastatin lay entirely within the acceptance range for bioequivalence (80%, 125%).

Table 5. Statistical Summary of Treatment Comparisons for Plasma Atorvastatin Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>PK Parameter³ (units)</th>
<th>Adjusted Geometric Mean</th>
<th>Ratio of Adjusted Geometric Means³</th>
<th>90% CI for Ratio³</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{\text{inf}} ) (ng h/mL)</td>
<td>131.13</td>
<td>124.03</td>
<td>105.73</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{max}} ) (ng h/mL)</td>
<td>127.49</td>
<td>120.79</td>
<td>105.55</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>29.24</td>
<td>28.85</td>
<td>101.37</td>
</tr>
</tbody>
</table>

³ Geometric mean (coefficient of variation %) for all PK parameters.

Geometric mean \( \text{AUC}_{\text{inf}} \) and \( C_{\text{max}} \), median \( T_{\text{max}} \), and mean \( t_{1/2} \) of ortho-hydroxyatorvastatin were similar for the new atorvastatin (two 40mg) and commercial atorvastatin (one 80mg) tablet formulations (Table S6). Geometric mean \( C_{\text{max}} \) and median \( T_{\text{max}} \) of para-hydroxyatorvastatin were similar for the new atorvastatin (two 40mg) and commercial atorvastatin (one 80mg) tablet formulations (Table S6). Geometric mean \( \text{AUC}_{\text{inf}} \) and \( t_{1/2} \) of para-hydroxyatorvastatin were not reported as less than 50% of subjects were evaluable for these parameters for both the new and commercial atorvastatin tablet formulations.

Safety data
There were no deaths or serious AEs reported in this study. Three subjects were permanently discontinued from the study due to AEs: 2 subjects after dosing with the commercial atorvastatin (one 80mg) tablet and 1 subject after dosing with the new atorvastatin (two 40mg) tablets. One subject was temporarily discontinued from the study due to an AE after dosing with the commercial atorvastatin (one 80mg) tablet.
A higher percentage of subjects reported all causality AEs after dosing with the new atorvastatin (two 40mg) tablets (19 [26.0%] subjects) than after dosing with the commercial atorvastatin (one 80mg) tablet (14 [18.7%] subjects). However, a similar number of subjects reported treatment-related AEs after dosing with the new atorvastatin (two 40mg) tablets (9 [12.3%] subjects) and after dosing with the commercial atorvastatin (one 80mg) tablet (9 [12.0%] subjects).

Overall, the AE profiles for both treatments in this study were consistent with the currently approved product information for commercial atorvastatin. The safety profile of both products seems to be comparable.

**Pharmacokinetics/Pharmacodynamics**

**PK/PD Pivotal Study (Study A2581172): An 8-Week, Open-Label, Phase 1 Study to Evaluate Pharmacokinetics, pharmacodynamics, Safety and Tolerability of Atorvastatin in Children and Adolescents with Heterozygous Familial Hypercholesterolemia (HeFH)**

**Objectives:**

**Primary objective:**
- To develop population pharmacokinetic (PK) models for atorvastatin and its active metabolites (ortho-hydroxyatorvastatin and para-hydroxyatorvastatin) in children and adolescents with HeFH, and to examine the influence of covariates on the PK parameters.

**Secondary objectives:**
- To assess the pharmacodynamic (PD) responses of atorvastatin in children and adolescents with HeFH, exploring the relationship between exposure and PD responses. The PD variables were LDL-C, TC, TG, HDL-C, VLDL-C, Apo A-1, and Apo B.
- To assess the safety and tolerability of atorvastatin in children and adolescents with HeFH.

**Tertiary objective:**
- To provide descriptive information on flow-mediated dilatation (FMD) of the brachial artery at Week 0 and at Week 8 in children and adolescents with HeFH, for whom consent for the procedure was given, at centres with established FMD facilities.

**Study Participants:**
A total of 39 children and adolescents, aged 6 to 17 years, were enrolled and treated with atorvastatin, with initial doses based on cohort age range. One cohort (Cohort A) included 15 patients, 6 to 12 years of age (mean = 8.7 years) and at Tanner Stage 1. The other cohort (Cohort B) included 24 patients, 10 to 17 years of age (mean = 13.5 years) and at Tanner Stage ≥2. All subjects had genetically confirmed HeFH and LDL-C ≥4 mmol/L at baseline. All subjects were Caucasian. The study included 20 males and 19 females. The mean body mass index (BMI) was 17.1kg/m² among Cohort A subjects, and 20.9kg/m² among Cohort B subjects. Subjects could take no concomitant medication, including antihyperlipidemic therapy, at study entry.
Treatments:
The initial dose of atorvastatin was 5mg daily of a chewable tablet for Cohort A and 10mg daily of a tablet formulation for the Cohort B. The starting doses were based on analyses of data from paediatric subjects with hypercholesterolemia (Study 981-147), and from a dose-response study in adult subjects (Study A2581042). The data indicate that a minimally efficacious effect of atorvastatin, defined as a 35% to 40% reduction in LDL-C, occurs within the dose range of 0.1 to 0.3 mg/kg, in both adults and children. World Health Organization (WHO) population height/weight charts show the average weight for 6- and 10-year-olds is approximately 20kg and 28kg, respectively. A 5mg starting dose in 6- to 10-year-old children would correspond to doses between 0.18 to 0.25mg/kg/day, which are within the effective dose range seen in adults and older children and adolescents.

The atorvastatin dose was permitted to be doubled if a subject had not attained target LDL-C of <3.35mmol/L based on data at Week 4 and if atorvastatin was well tolerated. Thus, subjects in Cohort A and Cohort B could have received an increased daily dose of atorvastatin 10mg (two 5-mg tablets) and 20mg (two 10-mg tablets), respectively.

Variables:
- **PK**: A sparse PK sampling approach was used in this study. At Weeks 2 and 6, a single blood sample was taken between 4 and 12 hours postdose. At Weeks 4 and 8, blood samples were collected predose and at 1 and 2 hours postdose. There were a total of 310 blood samples from the 39 subjects. Samples were analyzed for atorvastatin and active metabolites (o-hydroxyatorvastatin and p-hydroxyatorvastatin).
- **PD variables**: percent changes from baseline for the following lipid parameters: LDL-C, TC, TG, HDL-C, LDL-C/HDL-C Ratio, VLDL-C, Apo A-1, and Apo B. These assessments were required to be performed after a >10-hour fast. Blood samples were taken for the lipid profile assessments at Screening (Visit 1), Week 2 (Visit 3), Week 4 (Visit 4), Week 6 (Visit 5), and Week 8 (Visit 6).
- **FMD** was used to assess endothelial function in the brachial arteries by means of high-resolution ultrasound to measure arterial diameter responses to increased blood flow. FMD was assessed at Weeks 0 and 8. For each scan, baseline vessel diameter (mm), Peak vessel diameter (mm) and FMD (%) were entered into the FMD database. FMD was calculated from these parameters as:
  \[
  \text{FMD} = \left(\frac{\text{maximum diameter} - \text{baseline diameter}}{\text{baseline diameter}}\right) \times 100\%.
  \]

Statistical analysis:
Population PK analyses were conducted via non-linear mixed effects modelling. The concentrations of p-hydroxyatorvastatin were generally below the lower limit of quantification (LLQ) at the doses used in this trial, consistent with the results at the lower doses in adults; therefore, p-hydroxyatorvastatin was not included in the PK model. Exposure-response relationships were evaluated between atorvastatin, o-hydroxyatorvastatin, and atorvastatin plus o-hydroxyatorvastatin exposures and the PD endpoints (LDL-C, TC, and TG). Area under the concentration-time curve at steady state (AUCss) was utilized as the exposure metric.

The absolute and percent changes from baseline in the PD endpoints at Week 8 were analyzed for exposure-response relationship. The PD analysis population was defined as all enrolled subjects who received ≥1 dose of study drug and had ≥1 PD parameter measurement (ie, lipid values or FMD). Change and percent change from baseline in the
PD lipid parameters (LDL-C, TC, TG, HDL-C, LDLC/ HDL-C Ratio, VLDL-C, Apo A-1, and Apo B) were summarized using descriptive statistics (N, mean, median, SD, minimum, and maximum) by cohort over time. FMD was summarized using descriptive statistics (N, mean, median, SD, minimum, and maximum) by cohort and by centre.

**Results**

Of the 39 subjects who were treated with atorvastatin, including 15 in Cohort A and 24 in Cohort B, all completed the study. All treated subjects were analyzed for PD (efficacy) variables.

**Population PK Results:**

The paediatric PK dataset consisted of atorvastatin, o-hydroxyatorvastatin, and p-hydroxyatorvastatin plasma concentrations in 310 blood samples from 39 subjects, with weights ranging from 25 to 99kg. Age and weight distributions across Tanner Stages were consistent and lower in Tanner Stage 1 when compared to Tanner Stage ≥2 subjects. Renal and hepatic functions were within normal limits for all paediatric subjects. A combined parent-metabolite population PK model was developed, which utilized a 2-compartment model each with first-order absorption to describe atorvastatin PK and a 2-compartment model linked to the parent model to describe the o-hydroxyatorvastatin PK.

Atorvastatin apparent oral clearance (CL/F) was estimated at 699L/hr (95% CI, 570, 881L/hr) for the reference covariates Tanner Stage ≥2 and body weight of 70kg. Given the reference covariates (Tanner Stage ≥2 and 70kg weight), the population estimates (95%CI) of apparent atorvastatin central volume of distribution (Vc/F), apparent atorvastatin intercompartmental clearance (Q/F), apparent atorvastatin peripheral volume of distribution (Vp/F), absorption rate constant (Ka), apparent o-hydroxyatorvastatin clearance (CLm/fm), apparent o-hydroxyatorvastatin central volume of distribution (Vcm/fm), apparent o-hydroxyatorvastatin intercompartmental clearance (Qm/fm), apparent o-hydroxyatorvastatin peripheral volume of distribution (Vpm/fm), and relative bioavailability (F1) were 1020 (209, 2210) L, 227 (80.2, 470) L/hr, 1960 (1390, 2460) L, 0.200 (0.139, 0.304) hr⁻¹, 616 (248, 562) L/hr, 2040 (1740, 2250) L, and 1 (fixed), respectively. For those subjects at Tanner Stage 1, the typical estimate (95% CI) for relative bioavailability factor (F1) was 0.752 (0.577, 1.01).

Furthermore, atorvastatin CL/F appears to be similar in paediatric subjects compared to adults when allometrically scaled by subject weight. The estimated typical atorvastatin CL/F was 543L/hr for subjects with a body weight of 50kg (approximate group mean for Tanner Stage ≥2 subjects). The estimated typical atorvastatin CL/F was 553L/hr for subjects with a body weight of 35kg (approximate group mean for Tanner Stage 1 subjects).

After accounting for the effect of body weight on CL/F (for atorvastatin), Vc/F, Q/F, Vp/F, CLm/fm, Vcm/fm, Qm/fm, and Vpm/fm using an allometric power model, the addition of other covariates resulted in little improvement of the model fit and unexplained interindividual variability. The interindividual variabilities were atorvastatin CL/F (46.3%CV), Vc/F (106%CV), and CLm/fm (43.3%CV). Residual variability in both atorvastatin and o-hydroxyatorvastatin concentrations was approximately 40%CV.
Exposure-Response Results:
An exploratory exposure-response analysis evaluated the relationship between atorvastatin, o-hydroxyatorvastatin, and atorvastatin+o-hydroxyatorvastatin exposure and the PD endpoints (LDL-C, TC, and TG). AUCss was utilized as the exposure metric to explore correlations with the absolute and percent change at Week 8 in the PD endpoints. The exploratory analysis demonstrated a consistent absolute decrease in LDL-C and TC across all patients and a decrease in TG for most patients. 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 in the current study. In addition, there did not appear to be any evidence of variations in pharmacodynamic effects between Tanner Stage patients or across the range of atorvastatin and/or o-hydroxyatorvastatin exposures. This is likely due to the Tanner-stage dependent doses and the titration dosing design in this study, wherein the patients were evaluated for dose escalation based on target levels or reduction in LDL.

Table 6. Percent change in LDL-C at week 8 plotted versus atorvastatin, o-hydroxyatorvastatin and atorvastatin+o-hydroxyatorvastatin AUCss. The plot symbol denotes Tanner stage with Tanner stage 1 as open triangles and Tanner stage 2 as solid circles. The blue line is a local regression fit trend line and the dotted red lines represent the 95% confidence interval for the local regression fit.
PD Results:
Results of the parameters measured are presented in the tables below:

Table 7. Descriptive statistics for LDL-C (mmol/L) by visit and final dose assignment.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Tanner Stage 1</th>
<th>Tanner Stage ≥2</th>
<th>Atorvastatin Dose (After Titration Between Weeks 4 and 6)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Subjects who Stayed at 5 mg</td>
<td>Subjects who Increased to 10 mg</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>Subjects who Stayed at 5 mg</td>
<td>Subjects who increased to 10 mg</td>
</tr>
<tr>
<td>Baseline</td>
<td>5</td>
<td>4.87 (0.48)</td>
<td>4.7 (1.10)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>4.4, 5.6</td>
<td>4.7, 8.2</td>
</tr>
<tr>
<td>Week 2</td>
<td>Mean (SD)</td>
<td>3.12 (0.92)</td>
<td>4.75 (1.02)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>2.1, 4.3</td>
<td>2.9, 6.2</td>
</tr>
<tr>
<td>Mean % change from baseline (SD)</td>
<td>-6.27 (14.72)</td>
<td>-25.70 (7.76)</td>
<td>-29.22 (11.28)</td>
</tr>
<tr>
<td>Week 4</td>
<td>Mean (SD)</td>
<td>2.80 (0.40)</td>
<td>4.43 (0.80)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>2.3, 3.2</td>
<td>3.4, 5.7</td>
</tr>
<tr>
<td>Mean % change from baseline (SD)</td>
<td>-42.33 (8.24)</td>
<td>-30.27 (5.72)</td>
<td>-34.29 (8.67)</td>
</tr>
<tr>
<td>Week 6</td>
<td>Mean (SD)</td>
<td>2.97 (0.44)</td>
<td>3.80 (0.64)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>2.2, 3.3</td>
<td>3.0, 4.8</td>
</tr>
<tr>
<td>Mean % change from baseline (SD)</td>
<td>-38.87 (7.84)</td>
<td>-40.61 (6.34)</td>
<td>-59.63 (6.61)</td>
</tr>
<tr>
<td>Week 8</td>
<td>Mean (SD)</td>
<td>3.06 (0.54)</td>
<td>3.66 (0.80)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>2.3, 3.6</td>
<td>2.7, 4.8</td>
</tr>
<tr>
<td>Mean % change from baseline (SD)</td>
<td>-36.78 (11.16)</td>
<td>-42.70 (6.45)</td>
<td>-40.72 (8.41)</td>
</tr>
</tbody>
</table>

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum
* Upon review of a subject's Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well-tolerated, a subject's dose could be doubled at 3 days (±1 day) after the Week 4 visit.
### Table 8. Descriptive statistics for Total Cholesterol (mmol/L) by visit and final dose assignment.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>Tanner Stage 1</th>
<th>Tanner Stage ≥2</th>
<th>Atorvastatin Dose (After Titration Between Weeks 4 and 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects who Stayed at 5 mg</td>
<td>Subjects who Increased to 10 mg</td>
<td>All Tanner 1 Subjects</td>
<td>Subjects who Stayed at 10 mg</td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>6.76 (0.46)</td>
<td>8.58 (1.06)</td>
<td>7.97 (1.25)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>6.3, 7.3</td>
<td>7.0, 10.4</td>
<td>6.3, 10.4</td>
</tr>
<tr>
<td>Week 2</td>
<td>Mean (SD)</td>
<td>4.87 (0.92)</td>
<td>6.55 (1.27)</td>
<td>5.99 (1.39)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>4.1, 6.4</td>
<td>4.1, 8.2</td>
<td>4.1, 8.2</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>-28.06</td>
<td>-24.11</td>
<td>-25.43</td>
</tr>
<tr>
<td>Week 4</td>
<td>Mean (SD)</td>
<td>4.49 (0.41)</td>
<td>6.34 (0.84)</td>
<td>5.72 (1.15)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>4.0, 5.0</td>
<td>5.0, 7.4</td>
<td>4.0, 7.4</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>-33.37</td>
<td>-26.12</td>
<td>-28.54</td>
</tr>
<tr>
<td>Week 6</td>
<td>Mean (SD)</td>
<td>4.73 (0.60)</td>
<td>5.72 (0.75)</td>
<td>5.39 (0.83)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>3.8, 5.2</td>
<td>4.6, 7.0</td>
<td>3.8, 7.0</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>-29.99</td>
<td>-33.12</td>
<td>-32.08</td>
</tr>
<tr>
<td>Week 8</td>
<td>Mean (SD)</td>
<td>4.87 (0.39)</td>
<td>5.39 (0.75)</td>
<td>5.21 (0.69)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>4.4, 5.4</td>
<td>4.3, 6.6</td>
<td>4.3, 6.6</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>-27.80</td>
<td>-37.17</td>
<td>-34.05</td>
</tr>
</tbody>
</table>

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum.

* Upon review of a subject’s Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject’s dose could be doubled at 3 days (±1 day) after the Week 4 visit.
Table 9. Descriptive statistics for Tryglycerides (mmol/L) by visit and final dose assignment.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Statistic</th>
<th>Subjects who Stayed at 5 mg</th>
<th>Subjects who Increased to 10 mg</th>
<th>All Tanner 1 Subjects</th>
<th>Subjects who Stayed at 10 mg</th>
<th>Subjects who Increased to 20 mg</th>
<th>All Tanner ≥2 Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Min, max</td>
<td>Mean (SD)</td>
<td>N</td>
<td>Mean (SD)</td>
<td>N</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>1.01 (0.37)</td>
<td>1.20 (0.50)</td>
<td>1.14 (0.46)</td>
<td>0.5, 1.6</td>
<td>0.7, 2.3</td>
<td>0.5, 2.3</td>
</tr>
<tr>
<td>Mean</td>
<td>0.6, 0.9</td>
<td>0.5, 1.4</td>
<td>0.5, 1.4</td>
<td>0.5, 1.4</td>
<td>0.5, 1.7</td>
<td>0.5, 2.8</td>
<td>0.5, 2.8</td>
</tr>
<tr>
<td>Week 2</td>
<td>Mean (SD)</td>
<td>0.81 (0.39)</td>
<td>0.87 (0.30)</td>
<td>0.85 (0.32)</td>
<td>0.5, 1.7</td>
<td>0.5, 2.8</td>
<td>0.5, 2.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.5, 1.5</td>
<td>0.5, 1.4</td>
<td>0.5, 1.5</td>
<td>0.5, 1.5</td>
<td>0.5, 1.7</td>
<td>0.5, 2.8</td>
<td>0.5, 2.8</td>
</tr>
<tr>
<td>Mean</td>
<td>5.60</td>
<td>-0.87</td>
<td>-2.09</td>
<td>(38.26)</td>
<td>(29.06)</td>
<td>(31.61)</td>
<td>28.37</td>
</tr>
<tr>
<td>change from baseline (SD)</td>
<td>10.29</td>
<td>10.29</td>
<td>10.29</td>
<td>58.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Mean (SD)</td>
<td>0.71 (0.20)</td>
<td>0.69 (0.17)</td>
<td>0.70 (0.21)</td>
<td>0.5, 1.7</td>
<td>0.5, 2.5</td>
<td>0.5, 2.5</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.4, 1.1</td>
<td>0.5, 1.0</td>
<td>0.4, 1.1</td>
<td>0.5, 1.7</td>
<td>0.5, 1.7</td>
<td>0.5, 2.5</td>
<td>0.5, 2.5</td>
</tr>
<tr>
<td>Mean</td>
<td>-8.30</td>
<td>-21.43</td>
<td>-16.35</td>
<td>(32.55)</td>
<td>(30.42)</td>
<td>(30.87)</td>
<td>1.27</td>
</tr>
<tr>
<td>change from baseline (SD)</td>
<td>36.34</td>
<td>36.34</td>
<td>36.34</td>
<td>36.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>Mean (SD)</td>
<td>1.17 (0.60)</td>
<td>0.91 (0.27)</td>
<td>1.00 (0.40)</td>
<td>0.6, 1.5</td>
<td>0.4, 2.1</td>
<td>0.4, 2.1</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.5, 2.1</td>
<td>0.6, 1.3</td>
<td>0.5, 2.1</td>
<td>0.6, 1.5</td>
<td>0.4, 2.1</td>
<td>0.4, 2.1</td>
<td>0.4, 2.1</td>
</tr>
<tr>
<td>Mean</td>
<td>57.06</td>
<td>-1.27</td>
<td>18.18</td>
<td>(78.73)</td>
<td>(23.91)</td>
<td>(54.30)</td>
<td>-4.43</td>
</tr>
<tr>
<td>change from baseline (SD)</td>
<td>27.25</td>
<td>27.25</td>
<td>27.25</td>
<td>27.25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>Mean (SD)</td>
<td>0.79 (0.34)</td>
<td>0.79 (0.23)</td>
<td>0.79 (0.26)</td>
<td>0.5, 1.2</td>
<td>0.5, 1.8</td>
<td>0.5, 1.8</td>
</tr>
<tr>
<td>Min, max</td>
<td>0.5, 1.4</td>
<td>0.5, 1.2</td>
<td>0.5, 1.4</td>
<td>0.5, 1.2</td>
<td>0.5, 1.8</td>
<td>0.5, 1.8</td>
<td>0.5, 1.8</td>
</tr>
<tr>
<td>Mean</td>
<td>1.69</td>
<td>-0.88</td>
<td>-0.02</td>
<td>(31.48)</td>
<td>(33.31)</td>
<td>(32.06)</td>
<td>-20.94</td>
</tr>
<tr>
<td>change from baseline (SD)</td>
<td>29.69</td>
<td>29.69</td>
<td>29.69</td>
<td>29.69</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To meet the blood draw window (8 to 12 hours postdose), 5 Tanner 1 subjects and 1 Tanner ≥2 subject deviated from the protocol specification of dosing at 7 to 10 AM by taking their dose at midnight prior to the Week 2 visit. These subjects were noted on the Administration Schedule as having received a double dose, since they took 2 doses on the day the Week 2 visit.

SD = standard deviation; min = minimum; max = maximum.

* Upon review of a subject’s Week 4 low-density lipoprotein cholesterol data by the investigator, if target values were not attained and atorvastatin was well tolerated, a subject’s dose could be doubled at 5 days (±1 day) after the Week 4 visit.
Table 10. Descriptive statistics for HDL-C (mmol/L) by visit and final dose assignment.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Tanner Stage 1</th>
<th>Tanner Stage ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atorvastatin Dose (After Titration Between Weeks 4 and 6)*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subjects who Stayed at 5 mg</td>
<td>Subjects who Increased to 10 mg</td>
</tr>
<tr>
<td>N</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean (SD)</td>
<td>1.35 (0.12)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>1.2, 1.5</td>
</tr>
<tr>
<td>Week 2</td>
<td>Mean (SD)</td>
<td>1.43 (0.31)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>1.1, 1.8</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>5.38</td>
</tr>
<tr>
<td>Week 4</td>
<td>Mean (SD)</td>
<td>1.32 (0.16)</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>1.1, 1.5</td>
</tr>
<tr>
<td></td>
<td>Mean % change from baseline (SD)</td>
<td>-1.99 (3.90)</td>
</tr>
</tbody>
</table>

FMD values for subjects in Cohort A ranged from 0.0% to 11.5% at baseline and from 0.0% to 12.0% at Week 8. Similarly, the FMD values for subjects in Cohort B ranged widely, from 0.0% to 10.0% at baseline and from 2.9% to 9.3% at Week 8.

Discussion of the results

The most important finding in the population PK analysis was that atorvastatin clearance (CL/F) appears similar in paediatric subjects compared with adults when scaled by subject weight and that body weight was the only covariate influencing atorvastatin CL/F. Other covariates such as age, gender and Tanner stage had little influence on the PK parameters tested. The interindividual variability of the main PK parameters in the study was high but this does not invalidate the main conclusions.

Results of the exploratory PK/PD analysis assessing the relationship between AUCss of atorvastatin and PD endpoints (LDL-C, TC, and TG) shows a percent change from baseline in LDL-C and TC of approximately 40% and 30%, respectively, at the exposure level reached with the tested doses.

Study A2581172 demonstrated a clinically relevant reduction in lipid parameters from baseline to the end of week 8 in all cohorts. The measurements of FMD were non-conclusive.

For the efficacy part of the study the number of study subjects is small, especially the number of children below the age of 10 years. As the study is small, open, and not placebo
controlled the results regarding efficacy are of limited value. The small number of subjects did not allow for comparative statistical analyses.

The mean % change from baseline for LDL-C (mmol/L) after 8 weeks of treatment was between 35-40% in both cohorts of patients. The mean baseline LDL-C was higher in those patients who needed to double the dose after 4 weeks of treatment vs. those who did not need a dose adjustment (6.37 vs. 4.87 in Cohort A and 6.23 vs. 5.11 in cohort B), but in both subgroups the final mean % change from baseline was similar after the 8 week treatment period. The final absolute value was also of the same range; although in the subgroup of patients who needed an increased dose the final level was slightly higher than the target LDL-C of 3.35mmol/L. In this patient population with higher LDL-C baseline levels a higher dose than the ones used in the trial (10mg/20mg) could be necessary to achieve the LDL-C target, particularly in case of patients with high risk for developing cardiovascular disease. Greater reductions in lipid parameters with increasing doses were observed, but the desirable treatment goal for LDL according to the AHA guidelines was not reached for the treated groups. The TC changes are also of the same range in both cohorts but the effect over TG and HDL is not so consistent between the low and higher doses.

1.1.3 Clinical efficacy
Three supportive studies have been submitted: Study 981-147, Study 981-336 and Study 981-080.

Study 981-147: A 1-Year Study in Children and Adolescents With Familial or Severe Hypercholesterolemia Comparing Atorvastatin to Placebo (6-Month Double-Blind Treatment), Followed by Atorvastatin Open-Label Treatment for 6 Months

Objectives:
- To demonstrate the safety and efficacy of atorvastatin in decreasing elevated lipid levels in children and adolescents between 10 and 17 years of age who had familial hypercholesterolemia (FH) or severe hypercholesterolemia.

Population:
187 boys and postmenarchal girls 10 to 17 years of age (mean age, 14.1 years) with FH or severe hypercholesterolemia. Subjects qualified for the study were those with known FH or severe hypercholesterolemia and (1) LDL-C ≥4.91mmol/L (190mg/dL) or (2) LDL-C ≥4.14mmol/L (160mg/dL) and positive family history of FH or documented premature cardiovascular disease in a first- or second-degree relative.

Treatments:
After a 4-week placebo run-in, subjects were randomized to receive either placebo (n = 47) or atorvastatin 10mg (n = 140) in a double-blind fashion once daily for 6 months. The study drug could be titrated to 20mg at Week 4 if the subject’s LDL-C was ≥130mg/dL. The double-blind phase was followed by a 6-month atorvastatin open-label extension. All subjects received atorvastatin 10mg during the open-label extension phase. Therefore, the 76 subjects in the atorvastatin treatment group who were being treated with atorvastatin 20mg at Week 26 of the double-blind phase had their dose reduced to 10mg during the open-label phase. The placebo-treated subjects from the double-blind phase who continued into the open-label phase received 10mg of atorvastatin.
Variables:
The primary efficacy variable was the percent change from baseline in LDL-C at Week 26 (Endpoint Analysis). The secondary efficacy variables included the percent change from baseline in TC, TG, HDL-C, Apo A-1, and Apo B at Week 4 and Endpoint.

Statistical analysis:
For the Endpoint Analysis the last double-blind observation was carried forward to Week 26 for subjects who did not complete the 6-month double-blind phase of the study. Four subjects (3 [2.1%] atorvastatin, 1 [2.1%] placebo) discontinued early from the double-blind phase. Thus, data were summarized by Endpoint Analysis for all 187 subjects who received atorvastatin and by Week 26 for evaluable subjects enrolled through the end of the double-blind phase. Baseline was defined as the mean of the two values at Weeks -2 and 0. Analysis of covariance (ANCOVA) was performed to compare the effects of atorvastatin and placebo on the primary efficacy variable with a model that included the effects of treatment, centre, sex, baseline Tanner Stage, and the baseline value as a covariate. Each interaction was added separately to the main effects model and the Type III SS F-test p-value for each term was presented. The effect of atorvastatin and placebo on the primary efficacy variable was also compared using the Wilcoxon Rank Sum Test. This test was also used to assess the change from baseline in the secondary efficacy variables at Weeks 4 and 26. Data from the open-label phase of the study were analyzed based on length of atorvastatin therapy, and included treatment in the double-blind phase and open-label extension phase. Baseline in these analyses was the last visit before the start of atorvastatin.

Results:
Table 11. Study 981-147: Summary of changes in LDL-C during the double-blind phase.

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Atorvastatin Treatment Group</th>
<th>Placebo Treatment Group</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 4</td>
<td>N=138</td>
<td>N=47</td>
<td></td>
</tr>
<tr>
<td>Baseline (mg/dL)</td>
<td>218.9 ± 3.6</td>
<td>230.0 ± 6.9</td>
<td></td>
</tr>
<tr>
<td>Week 4 (mg/dL)</td>
<td>141.9 ± 3.0</td>
<td>221.8 ± 6.3</td>
<td></td>
</tr>
<tr>
<td>Mean percent change</td>
<td>-35.0 ± 0.9</td>
<td>-2.8 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>LS mean percent changea</td>
<td>-35.0 ± 2.6</td>
<td>-2.1 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpointb</td>
<td>N=140</td>
<td>N=47</td>
<td></td>
</tr>
<tr>
<td>Baseline (mg/dL)</td>
<td>218.6 ± 3.6</td>
<td>230.0 ± 6.9</td>
<td></td>
</tr>
<tr>
<td>Endpoint (mg/dL)</td>
<td>130.7 ± 2.8</td>
<td>228.5 ± 8.0</td>
<td></td>
</tr>
<tr>
<td>Mean percent change</td>
<td>-39.6 ± 1.1</td>
<td>-0.4 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>LS mean percent changea</td>
<td>-40.0 ± 3.3</td>
<td>-0.4 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a Values are mean ± standard error.

b Type III SS F-test for percent change controlling for center, sex, baseline Tanner Stage, and baseline LDL-C.

c Adjusted for center, sex, baseline Tanner Stage, and baseline LDL-C.

d Endpoint = Week 26 data or the last double-blind observation carried forward to Week 26 for subjects who did not complete the 6 month double-blind phase.

Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number; LS=least squares.
Source: Study 981-147 Clinical Study Report.
Table 12. Study 981-147: Summary of changes in secondary efficacy variables at endpoint during the double-blind phase.

<table>
<thead>
<tr>
<th>Statistica</th>
<th>Atorvastatin Treatment Group</th>
<th>Placebo Treatment Group</th>
<th>F Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>140</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>Baseline (mg/dL) 285.0 ± 3.8</td>
<td>297.5 ± 7.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint (mg/dL) 294.0 ± 3.1</td>
<td>293.2 ± 6.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean percent change -31.4 ± 1.0</td>
<td>-1.5 ± 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean percent change -32.3 ± 2.7</td>
<td>-2.0 ± 3.1</td>
<td>-6.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>Baseline (mg/dL) 45.8 ± 0.8</td>
<td>46.2 ± 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint (mg/dL) 46.7 ± 0.9</td>
<td>45.0 ± 1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean percent change 2.6 ± 1.3</td>
<td>-1.9 ± 1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean percent change -2.4 ± 1.4</td>
<td>-8.0 ± 3.9</td>
<td>0.022</td>
</tr>
<tr>
<td>TG</td>
<td>Baseline (mg/dL) 103.2 ± 4.9</td>
<td>100.0 ± 8.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint (mg/dL) 83.2 ± 2.7</td>
<td>98.4 ± 7.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean percent change -12.0 ± 3.9</td>
<td>1.6 ± 6.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean percent change -12.0 ± 5.4</td>
<td>1.0 ± 9.3</td>
<td>0.029</td>
</tr>
<tr>
<td>Apo A1</td>
<td>Baseline (mg/dL) 325.4 ± 3.6</td>
<td>324.6 ± 3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint (mg/dL) 229.0 ± 2.0</td>
<td>225.3 ± 2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean percent change 5.4 ± 2.0</td>
<td>1.3 ± 1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean percent change -1.6 ± 3.3</td>
<td>-4.4 ± 3.7</td>
<td>0.790</td>
</tr>
<tr>
<td>Apo B</td>
<td>Baseline (mg/dL) 380.4 ± 2.2</td>
<td>392.5 ± 2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint (mg/dL) 321.0 ± 2.2</td>
<td>195.1 ± 6.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean percent change -34.0 ± 1.1</td>
<td>0.7 ± 1.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LS mean percent change -32.5 ± 2.9</td>
<td>2.2 ± 3.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Value are mean ± standard error.
* Type III SS F-test for per-protocol change controlling for center, sex, baseline Tanner Stage, and baseline LDL-C.
* Adjusted for center, sex, baseline Tanner Stage, and baseline LDL-C.
* Endpoint = Week 26 data or the last double-blind observation carried forward to Week 26 for subjects who did not complete the 6-month double-blind phase.
* Abbreviations: N=number; LS=least squares; TC=total cholesterol; HDL-C=high density lipoprotein cholesterol; TG=triglycerides; Apo A1=apolipoprotein A1; Apo B=apolipoprotein B.
* Source: Study 981-147 Clinical Study Report.

Table 13. Study 981-147: Summary of change in LDL-C and percentage of subjects who reached the targeted goal of LDL-C < 130 mg/dL during the open-label phase.

<table>
<thead>
<tr>
<th>Statisticc</th>
<th>Week 20 (End of Double-Blind Phase)</th>
<th>Week 52 (Double Blind – Open Label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>135</td>
<td>122</td>
</tr>
<tr>
<td>Baseline (mg/dL) 218.6 ± 3.6</td>
<td>219.9 ± 3.7</td>
<td></td>
</tr>
<tr>
<td>Visit Value (mg/dL) 129.1 ± 2.7</td>
<td>143.4 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Mean Percent Change -40.3 ± 1.1</td>
<td>-54.3 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Percent Subjects at Goald</td>
<td>60.6%</td>
<td>43.0%</td>
</tr>
<tr>
<td>35% CI</td>
<td>48.8 – 71.4%</td>
<td>32.8 – 55.1%</td>
</tr>
</tbody>
</table>

* Mean ± standard error.
* For the subjects who received atorvastatin in the double-blind phase and continued into the open-label phase; 70 of 132 subjects included in the analysis at the end of the open-label period underwent a reduction in dose from atorvastatin 20 mg daily to 10 mg daily.
* Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number; CI=confidence interval.
* Source: Study 981-147 Clinical Study Report.

Discussion of results
The study population was not entirely homogeneous, being both subjects with HeFH and hypercholesterolemia of other causes. After week 4, an increase of the dose was necessary in approximately 58% of patients who did not reach the target threshold. At week 26, a statistically significant effect is observed in reducing the LDL-C level with a 60% percent of patients reaching the targeted goal of <130mg/dL. Also a statistically significant effect is observed in the majority of the lipid parameters (TC, HDL-C, TG, Apo-B). The 10mg dose was administered to all patients during the open-label phase and the target goal was reached in 44% of patients during this period. During the open-label phase the slight lowering of the
efficacy was expected because 76 atorvastatin-treated subjects receiving 20mg daily during the double-blind phase had their dose reduced to 10mg daily for the open-label phase. Dosing was not weight adjusted, but a fixed amount of drug was given depending on age, and the dose increased if clinical effect was not adequate. This study provides the strongest evidence for dosing recommendations.

Study 981-336: A 1 Year, Open-Label, Randomized Parallel Group Multicentre Study for the Comparison of Atorvastatin vs. Colestipol on the Treatment of Children and Adolescents with Familial Hypercholesterolemia (FH) and Hypercholesterolemia

Objective:
• To compare the safety and efficacy of atorvastatin versus colestipol in decreasing elevated lipid levels in children and adolescents between 10 and 18 years of age who have FH and hypercholesterolemia.

Population:
The study population consisted of 56 subjects, of whom 25 subjects were randomized to receive atorvastatin and 31 subjects to receive colestipol.

Treatments:
Patients received either atorvastatin 10mg daily or colestipol 5g daily according a randomized code, and stratified according to the sex of the patient. The daily dose could have been increased to atorvastatin 20mg or colestipol 10g at Week 6 based on a target LDL-C level of ≥130mg/dL. At Week 12 the doses could have been further increased to atorvastatin 40mg or colestipol 20g based on a target LDL-C level of <130mg/dL. Patients were to remain on the dose prescribed at Week 12 through week 52, unless modified for reasons of safety or efficacy.

Variables:
The primary efficacy variable was LDL-C at Week 26. The baseline value was defined as the mean of two values from study Weeks -2 and 0. The secondary efficacy variables were percent change from baseline in LDL-C at Week 52, and percent change from baseline in TC, TG, HDL-C, VLDL-C, TC/HDL-C Ratio, and LDL-C/HDL-C Ratio at Weeks 26 and 52. In addition, the percentage of patients reaching goal (defined as LDL-C <130mg/dL) was determined at Weeks 26 and 52.

Statistical analysis:
Three sub-populations were used for the analyses: safety population, intent-to-treat (ITT) population, and per protocol (PP) population. The ITT population included subjects who were randomized, received at least one dose of study medication, and had at least one post-baseline efficacy measure. The PP population included subjects in the ITT population who met the following additional criteria:
• Between 10 and 18 years of age;
• Tanner Stage ≥2 at screening visit;
• LDL-C ≥5.2mmol/L (200mg/dL) at baseline;
• TG ≤2.25mmol/L (200mg/dL; mean of values at two baseline visits); and
• Received no prohibited medication at screening or any time during the study.

The safety population and the ITT population consisted of the 56 randomized subjects, and PP population comprised 45 subjects.
Results:
An overview of the results can be found in the tables below:

Table 14. Study 981-336: Percent change from baseline in LDL-C at week 26.

<table>
<thead>
<tr>
<th>Statistic*</th>
<th>Atorvastatin</th>
<th>Colestipol</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Baseline (mg/dL)</td>
<td>253.3 ± 48.4</td>
<td>232.3 ± 48.4</td>
</tr>
<tr>
<td>Week 26 (mg/dL)</td>
<td>146.5 ± 38.3</td>
<td>189.5 ± 38.5</td>
</tr>
<tr>
<td>% Change from Baseline</td>
<td>-38.2 ± 16.2</td>
<td>-21.2 ± 16.2</td>
</tr>
<tr>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

Per Protocol Population

<table>
<thead>
<tr>
<th>Statistic*</th>
<th>Atorvastatin</th>
<th>Colestipol</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>23</td>
<td>22</td>
</tr>
<tr>
<td>Baseline (mg/dL)</td>
<td>260.1 ± 39.0</td>
<td>248.7 ± 39.9</td>
</tr>
<tr>
<td>Week 26 (mg/dL)</td>
<td>147.2 ± 40.4</td>
<td>192.6 ± 41.0</td>
</tr>
<tr>
<td>% Change from Baseline</td>
<td>-40.7 ± 17.3</td>
<td>-23.0 ± 17.3</td>
</tr>
<tr>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0012</td>
<td></td>
</tr>
</tbody>
</table>

* Mean ± standard deviation.
Abbreviations: LDL-C=low-density lipoprotein cholesterol, N=number.
Source: Study 981-336 Clinical Study Report
Table 15. Study 981-336: Summary of secondary efficacy variables: LDL-C at week 52, and TC, TG, HDL-C and VLDL-C at weeks 26 and 52.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistica</th>
<th>Atorvastatin</th>
<th>Colestipol</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>Baseline</td>
<td>253.8 (48.4)</td>
<td>232.3 (48.4)</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>&lt;0.0001</td>
<td>0.1024</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>129.3 (39.5)</td>
<td>191.7 (40.1)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-10.8 (13.9)</td>
<td>-19.7 (16.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>Baseline</td>
<td>307.1 (49.1)</td>
<td>293.3 (49.1)</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.193</td>
<td>0.2983</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>199.9 (38.7)</td>
<td>247.4 (38.9)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-32.5 (12.9)</td>
<td>-17.0 (12.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>194.5 (36.0)</td>
<td>251.1 (36.2)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-34.2 (11.8)</td>
<td>-15.4 (11.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>Baseline</td>
<td>69.9 (27.8)</td>
<td>79.1 (27.8)</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.1504</td>
<td>0.1504</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>66.4 (25.7)</td>
<td>84.9 (25.7)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-11.1 (38.6)</td>
<td>-13.3 (38.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.0672</td>
<td>0.0315</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0052</td>
<td>0.0052</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>62.6 (28.5)</td>
<td>84.4 (28.5)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-15.2 (44.8)</td>
<td>-12.0 (44.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.0125</td>
<td>0.0469</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0014</td>
<td>0.0014</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>Baseline</td>
<td>44.7 (10.2)</td>
<td>48.5 (10.2)</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.1446</td>
<td>0.1446</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>46.6 (8.5)</td>
<td>49.6 (8.4)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>0.8 (18.6)</td>
<td>7.4 (18.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.8413</td>
<td>0.0332</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.1890</td>
<td>0.1890</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>47.0 (8.9)</td>
<td>47.4 (8.9)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>2.3 (18.6)</td>
<td>2.7 (18.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.5512</td>
<td>0.4859</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.9849</td>
<td>0.9849</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>Baseline</td>
<td>8.5 (7.4)</td>
<td>10.7 (7.5)</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.2364</td>
<td>0.2364</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>6.3 (5.4)</td>
<td>11.4 (5.4)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-34.3 (128.6)</td>
<td>18.7 (128.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.0015</td>
<td>0.1132</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0004</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>7.7 (6.2)</td>
<td>12.8 (6.2)</td>
</tr>
<tr>
<td>% Change from baseline</td>
<td>-19.4 (173.4)</td>
<td>35.7 (173.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p-value (% change from baseline)</td>
<td>0.0059</td>
<td>0.0059</td>
</tr>
<tr>
<td></td>
<td>p-value (atorvastatin vs. colestipol)</td>
<td>0.0011</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

a Mean (standard deviation).

Abbreviations: LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; VLDL-C=very low-density lipoprotein cholesterol; N=number.

Source: Study 981-336 Clinical Study Report.

Ten of 25 (40%) atorvastatin-treated subjects and five of 31 (16.1%) colestipol-treated subjects had LDL-C ≥130 mg/dL at Week 26 (p = 0.0630). Ten of 25 (40%) atorvastatin-treated subjects and two of 31 (6.5%) of colestipol-treated subjects had LDL-C ≥130mg/dL at Week 52 (p=0.0024).

Discussion of results
The LDL-C baseline level is slightly higher in this study than in the previous one. It is not clear if the patients included have HeFM, combined (mixed) familial hypercholesterolemia or other diagnosis.

The dose of atorvastatin/colestipol was allowed to be increased up to 40mg atorvastatin/20g colestipol during the first 12 weeks treatment period in case the targeted goal was not reached but the remained constant until the end of the study. The dose is titrated according
to effect on lipid parameters, but the dosing was not weight adjusted. The dose of atorvastatin in mg/kg is therefore very variable among study subject. At week 26 a statistically significant effect is observed in reducing the LDL-C level with a 40% percent of patients reaching the targeted goal of <130mg/dl in comparison with a 16% in the colestipol group. The response rate was maintained at week 52.

Study 981-080: A Multicentre, Open-Label, Compassionate-Use Study to Assess the Efficacy and Safety of Atorvastatin in Patients with Severe Hypercholesterolemia Who Have Not Achieved an Adequate Response with Conventional Lipid-Lowering Therapy

Study 981-080 was an 8-week, open-label, compassionate-use study with an optional extension phase of variable length.

Objective:
- To evaluate the efficacy and safety of atorvastatin in patients with severe hypercholesterolemia refractory to maximally tolerated lipid-lowering therapy.

Population:
Patients with confirmed homozygous familial hypercholesterolemia (HoFH) or non-homozygous severe hypercholesterolemia (SHC; LDL-C levels >200mg/dL while receiving maximally tolerated lipid-lowering therapy) were eligible for participation in the study. A total of 335 patients were enrolled; 89 patients were classified as having HoFH and the remaining 246 patients were classified as patients having non-homozygous severe hypercholesterolemia.

Overall patient age ranged from 2 to 73 years, with a mean age of 39 years. Patients with HoFH had a lower mean age than patients with SHC (24 years versus 45 years). Overall, most patients were 18 years or older (86%); the majority of patients under the age of 18 were in the HoFH patient group. Patients were primarily Caucasian (89%), and the percentage of male and female patients was nearly equal (54% male; 46% female).

Treatment:
Most patients enrolled in the study received atorvastatin 40mg daily for 4 weeks and were then titrated to 80mg daily for an additional 4 weeks. However, some patients began treatment with doses as low as 2.5mg daily and titrated as individually appropriate. Patients who responded to atorvastatin during the 8-week initial evaluation period were allowed to continue into the extension phase with safety and efficacy evaluations at regular intervals.

Variables:
The primary efficacy variable was the percent change in LDL-C from baseline levels to Week 8. Secondary efficacy variables included the percent change in TC, TG, and HDL-C from baseline levels to Week 8. Efficacy data were summarized for all patients, HoFH patients, and SHC patients, and data were compared for patients with HoFH versus those with SHC.
Results:
An overview of the results can be found in the table below:

Table 15. Study 981-080: Summary of primary (LDL-C) and secondary (TC, TG and HDL-C) efficacy variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic*</th>
<th>All</th>
<th>HoFH</th>
<th>SHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>N</td>
<td>328</td>
<td>88</td>
<td>240</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Baseline</td>
<td>388.1</td>
<td>525.3</td>
<td>355.0</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>265.6</td>
<td>410.1</td>
<td>239.6</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>-122.6</td>
<td>-115.3</td>
<td>-128.4</td>
</tr>
<tr>
<td>% Change</td>
<td>-52.1</td>
<td>-20.2</td>
<td>-36.2</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>N</td>
<td>327</td>
<td>88</td>
<td>239</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Baseline</td>
<td>458.2</td>
<td>585.7</td>
<td>415.5</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>326.1</td>
<td>462.0</td>
<td>376.2</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>-132.1</td>
<td>-123.7</td>
<td>-133.3</td>
</tr>
<tr>
<td>% Change</td>
<td>-28.1</td>
<td>-20.2</td>
<td>-32.1</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>N</td>
<td>327</td>
<td>88</td>
<td>239</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Baseline</td>
<td>198.6</td>
<td>139.9</td>
<td>220.5</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>132.1</td>
<td>106.6</td>
<td>141.7</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>-66.5</td>
<td>-33.9</td>
<td>-78.5</td>
</tr>
<tr>
<td>% Change</td>
<td>-22.6</td>
<td>-12.4</td>
<td>-26.2</td>
<td></td>
</tr>
<tr>
<td>HDL-C</td>
<td>N</td>
<td>326</td>
<td>88</td>
<td>238</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Baseline</td>
<td>37.4</td>
<td>32.4</td>
<td>39.2</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>38.2</td>
<td>32.2</td>
<td>40.4</td>
</tr>
<tr>
<td></td>
<td>Change</td>
<td>0.8</td>
<td>-0.2</td>
<td>1.2</td>
</tr>
<tr>
<td>% Change</td>
<td>5.2</td>
<td>5.4</td>
<td>6.1</td>
<td></td>
</tr>
</tbody>
</table>

*Mean (standard error).

Abbreviations: HmFH=homozogous familial hypercholesterolemia; SHC= non homozogous severe hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; N=number.

Source: Study 981-080 Clinical Study Report

Discussion of results
In this compassionate, open-label study patients with either confirmed homozygous FH or non-homozygous severe hypercholesterolemia were enrolled and were refractory to other lipid-lowering therapies. All patients had LDL> 200mg/dL. Fourteen percent (46) were children and adolescents. 89 patients were classified as having HoFH the majority of them under the age of 18. The LDL-C baseline level is higher in this study than in the previous ones. The % LDL-C change from baseline reached a 36% in the group of patients with non-homozygous hypercholesterolemia and a lower percentage (20%) in the group of patients with HoFH. Atorvastatin seems to have decreased efficacy in the homozygous FH group, so it is possible that patients with this variant may need higher atorvastatin doses.

Clinical safety
Safety data was presented for the four studies involving paediatric patients (pivotal study A2581172, and supportive studies 981-080, 981-147, and 981-336).

Adverse events
Due to the small number of paediatric studies and the non-homogenous coding of adverse events, the adverse event data from these studies has not been pooled. The data is presented by individual study.

Study 981-080 Compassionate use study in paediatric and adult subjects:
Twenty-seven of 46 paediatric patients reported AEs, 12 of which were considered treatment related. There were no treatment-related serious AEs. Due to the small number of paediatric patients in the study, all AEs were considered to be common as a single report would constitute an incidence rate of > 2%. There were no meaningful differences in adverse event profiles when the data were stratified by age. One death occurred in study
981-080: an 18-year-old Asian subject with a history of familial hypercholesterolemia was involved in a motor vehicle accident on study day 538 and died on study day 552 due to severe head injuries sustained during the accident. The patient had received 537 days of treatment with atorvastatin 40mg to 80mg QD; no concomitant medications were noted. The event was considered not related to atorvastatin.

**Study 981-147 A 52 week efficacy and safety study in patients 10-17 years:** The overall incidence of all causality adverse events reported during the double-blind phase was similar for the atorvastatin and placebo treatment groups (62.9% [88/140] and 61.7% [29/47], respectively).

An overview of the results can be found in the tables below:

**Table 16. Adverse events (all causality) occurring in ≥ 5% of subjects in either treatment group during the double-blind phase.**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Atorvastatin N (%)</th>
<th>Placebo N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number treated*</td>
<td>140 (100.0)</td>
<td>47 (100.0)</td>
</tr>
<tr>
<td>Number with adverse events*</td>
<td>88 (62.9)</td>
<td>29 (61.7)</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6 (4.3)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>13 (9.3)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (1.4)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>9 (6.4)</td>
<td>6 (12.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (9.3)</td>
<td>3 (6.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>27 (19.3)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9 (6.4)</td>
<td>3 (6.4)</td>
</tr>
</tbody>
</table>

*Number given is number of subjects  
**Subjects may have had more than one adverse event

In both treatment groups, the most common adverse events were those caused by illness or a sign of illness, such as infection, flu syndrome, pharyngitis or fever. The 88 subjects with adverse events in the atorvastatin group reported 176 events and the 29 subjects in the placebo group reported 58 events. The majority of these events in both the atorvastatin and placebo treatment groups were mild (93 [53%] and 34 [59%], respectively) or moderate (74 [42%] and 20 [34%], respectively), with only a few events severe (9 [5%] and 4 [7%], respectively). Severe events which occurred in both treatment groups included abdominal pain (one event in each treatment group) and vomiting (two and one events, respectively). Severe events that occurred only in the atorvastatin treatment group (incidence of one for each event) included infection, photosensitivity reaction, migraine, syncope, depression and dizziness. Severe events that occurred only in the placebo treatment group (incidence of one for each event) included accidental injury and dyspepsia.

The overall incidence of treatment-related adverse events was small in both the atorvastatin and placebo treatment groups during the double-blind phase (7.1% [10/140] and 4.3% [2/47], respectively). The majority of these events in both the atorvastatin and placebo treatment groups were mild or moderate, with one severe event in each treatment group.

**Study 981-336 A 52 week efficacy and safety study in patients 10-18 years:** Of the 25 subjects that received atorvastatin, a total of 14 (56.0%) subjects experienced at least one adverse event. Of the 31 subjects that received colestipol, 19 (61.3%) subjects experienced at least one adverse event. The most frequent adverse events in the atorvastatin group were: gastritis, two subjects, 8%; nasopharyngitis, two subjects, 8%; and cough, two subjects, 8%. The most frequent adverse events in the colestipol group were: tonsillitis, three subjects,
9.7%; abdominal pain, two subjects, 6.5%; nasopharyngitis, two subjects, 6.5%; pyrexia, two subjects, 6.5%; and ear infection, two subjects, 6.5%. One (4%) subject who received atorvastatin discontinued due to an adverse event of gastritis, and this was the only AE assessed as serious. No subjects who received colestipol experienced serious adverse events. The most frequent clinically significant laboratory abnormalities were in the atorvastatin group: blood bilirubin increased, one subject, 4%, and in the colestipol group: blood bilirubin increased, two subjects 6.5% and alanine aminotransferase increased, one subject 3.2%.

**Study A2581172 An 8 week PK/PD and safety study in subjects 6 to 17 years:** No deaths, other serious AEs, or severe AEs were reported in this study. In addition, no permanent or temporary discontinuations or dose reductions due to AEs occurred. Overall, all-causality AEs were experienced by 9 of 15 of the cohort A subjects and 13 of 24 of the cohort B subjects. Treatment-related AEs were observed for two of 15 cohort A subjects and two of 24 cohort B subjects. Overall (including subjects in both cohorts), the most frequently observed AEs in this study were nasopharyngitis (3 subjects), viral upper respiratory tract infection (3 subjects), gastroenteritis (2 subjects), ALT increased (2 subjects), and headache (3 subjects). Four subjects experienced treatment-related AEs, which included abdominal pain, nausea, vomiting, and headache experienced among two cohort A subjects, and ALT increased experienced by two cohort B subjects. Most AEs were mild and the remaining AEs were of moderate severity. Moderate severity AEs, including six AEs among cohort A subjects and three AEs among cohort B subjects, included AEs of viral upper respiratory tract infection, gastroenteritis, nausea, bronchopneumonia, lower respiratory tract infection bacterial, hand fracture, blood creatinine increased, asthma, and urticaria.

**Discussion on clinical safety**

The safety database in paediatric patients includes data from the pivotal and the three supportive trials. The majority of the paediatric patients received doses from 5 to 20mg in the pivotal and the two comparative trials and the longer treatment duration was one year. No new adverse events have been described. The specific body systems associated with a high number of events in the paediatric trials include the ‘digestive system’, the ‘respiratory system’ and the ‘infections and infestations’ group, reflecting inter-current illnesses that are common among paediatric patients or other AES already described in the product information.

Two cases of ALAT elevation in Study A2581172 are a potential concern (13-year old female on 10mg dose had ALAT level of 143U/L on day 29 – resolved without withdrawal of treatment). Another 13-year old female on 20mg dose had ALAT level of 52 U/L on final visit). In adult studies the overall incidence of ALAT elevation is only 0.5%. Larger treatment numbers are needed to address this issue. Hopefully, the ongoing A2581173 study (a 3-year study of the safety and follow-up study of efficacy of atorvastatin treatment of children and adolescents (aged 6 years to less than 18 years) with heterozygous familial hypercholesterolemia) will provide supportive safety data in this regard.

Another potential concern, not addressed in the trial cohorts, is the effect of off label use in children and adolescents with dietary (secondary) hypercholesterolemia and possible underlying fatty liver.
The majority of the paediatric patients were treated with 10mg to 20mg doses and the patient population exposed to the higher doses is small. Although the safety profile of atorvastatin is well-known, the safety information for paediatric patients treated with the higher doses is scarce. In particular, some adverse events are dose related, and data for paediatric exposure to the 80mg dose is limited to the compassionate use study (in which only 14% of the patient populations were children and not all of them were treated with this higher dose).

It is also noted that there is no information on the effect of long-term atorvastatin treatment on long-term growth or maturation parameters. Previous experience with other statins does not suggest any detrimental effect. The ongoing study A2581173 is expected to also provide useful information with respect to long-term growth and maturation.

Short term safety is adequately addressed but long term safety is unknown as of yet, especially for children below the age of 10 years.

1.2 PHARMACOVIGILANCE
Risk Management Plan
A consolidated version of a Risk Management Plan (RMP) was submitted for atorvastatin.

Safety Specification
Limitations of the human safety database:
Data of overall exposure to atorvastatin in clinical trials is presented. The only information that refers to population ≤18 years is number of persons (154 male and 80 female) and person-days of exposure (1745.35 male and 969.49 female), also differentiated by indication and design of the study. Other information (exposure by cumulative duration, by dose of maximum duration, by ethnic origin, in patients with renal disorders and in patients with cardiac impairment), is provided for overall population.
It has been estimated a total of 220,000 prescriptions for patients ≤17 years in post-marketing exposure (0.09%).
Safety and effectiveness of atorvastatin have been studied in a small number of patients younger than 18 years old, and have not been established for pregnant or lactating women.

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Persons</th>
<th>Person Months (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 years</td>
<td>7</td>
<td>13.87</td>
</tr>
<tr>
<td>6 - &lt;10 years</td>
<td>14</td>
<td>4.76</td>
</tr>
<tr>
<td>10 - ≤18</td>
<td>228</td>
<td>7.69</td>
</tr>
<tr>
<td>All ≤ 18</td>
<td>249</td>
<td>7.70</td>
</tr>
</tbody>
</table>

*Data generated 02 February 2010 to include patients from newly completed paediatric study A2581172

Table 18. Demographics for paediatric patients in clinical trials (n=249)*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>149</td>
</tr>
<tr>
<td>Female</td>
<td>100</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>221</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
</tr>
<tr>
<td>Asian</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
</tr>
</tbody>
</table>

*Data generated 02 February 2010 to include patients from newly completed paediatric study A2581172
Adverse events:
From the results of the clinical trials and the post marketing information submitted, the pediatriic safety profile is not foreseen to be significantly different from that of adults. Nevertheless, it is recognised that the information currently available is limited. The following risks have been listed as identified and potential risks for overall population, taking into account the last PSUR generated for atorvastatin:

<table>
<thead>
<tr>
<th>Safety Concern</th>
<th>Planned action(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyolysis and potential rhabdomyolysis-related events</td>
<td>Routine pharmacovigilance</td>
</tr>
<tr>
<td>Anger, aggression and irritability</td>
<td>Routine pharmacovigilance</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Routine pharmacovigilance</td>
</tr>
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<td>Interstitial lung disease / pneumonitis-related events</td>
<td>Routine pharmacovigilance</td>
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<td>Selected autoimmune events / Antinuclear antibody positive</td>
<td>Routine pharmacovigilance</td>
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<tr>
<td>Hepatic failure-related events</td>
<td>Routine pharmacovigilance</td>
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Pharmacovigilance Plan
The Marketing Authorisation Holder will evaluate all paediatric cases reported through the post marketing systems and perform cumulative reviews of paediatric cases on a quarterly basis.

The Marketing Authorisation Holder will also monitor closely all safety data generated from the ongoing study A2581173 (3-year study of the safety and follow-up study of efficacy of atorvastatin treatment of children and adolescents aged 6 years to less than 18 years with heterozygous familial hypercholesterolaemia) that is part of the approved PIP and is expected to be completed in 2014. Results should be available in the first quarter of 2015.

Evaluation of the need for a Risk Minimisation Plan
Wording has been agreed for inclusion in the SmPC to reflect the limited paediatric data available and advise the prescriber on appropriate starting doses and titration considerations in paediatric patients.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

1.3 BENEFIT-RISK BALANCE
1.3.1 Benefits
The efficacy of atorvastatin in reducing lipid parameters in children is analogous to the proved in the adult population. The effect observed in the percentage of change from baseline in LDL-C in paediatric patients is of same magnitude than in the adult population (35% to 40%) with the exception of patients with homozygous familial hypercholesterolemia (20%), although the same pattern is observed in the adult population given the high baseline LDL-C levels. The effect is consistent in both Tanner stage 1 and ≥ 2 and the exploratory PK/PD analysis shows that a similar effect is observed over the
ranges of exposures although the efficacy and safety data in children between the ages of 6-9 years are limited.

The safety profile in children appears to be similar to that described in adults. The AEs observed in the paediatric studies are similar to those included in the SPC for the adult population and no new AEs have been described.

The development of a paediatric specific pharmaceutical form promotes treatment compliance and facilitates the administration of doses appropriate to the paediatric patients.

1.3.2 Risks
The experience with the higher recommended doses and in the younger population is scarce and limited to patients with severe disease included in the compassionate use programme. Only 14 patients between 6 and <10 were exposed to the atorvastatin during clinical trials which is insufficient to consider safety and efficacy adequately demonstrated in this age group. Taking into account that some AEs are dose related, especially the hepatic and musculoskeletal disorders, there are safety concerns regarding the use in the population between 6 and <10 years.

Even in the paediatric patients over 10, information on the long-term safety profile is limited. No information is available on the effect of atorvastatin treatment on long-term growth or maturation parameters, although previous experience with other statins does not suggest any detrimental effect. The ongoing study A2581173 is expected to provide useful information with respect to long-term growth and maturation, as well as lipid parameters and safety profile in approximately 250 patients.

Experience with doses higher than 20mg is limited, and therefore so is the knowledge of the safety profile at high doses. Therefore it is appropriate that paediatric use should be restricted to this dose range and only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia.

1.3.3 Benefit-Risk Balance
In conclusion, the efficacy of atorvastatin in reducing lipid parameters in children is analogous to the proved in the adult population and the effect is consistent with the proposed posology. The safety profile in children appears to be similar to that described in adults, although long term safety is unknown, particularly for children below the age of 10 years and with the higher doses.

1.3.4 Risk management plan
The CHMP, having considered the data submitted, including the fact that a 3-year safety and efficacy study is already ongoing as agreed in the approved PIP, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information

1.3.5 Recommendation
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Lipitor 5mg, 10mg, 20mg and 40mg chewable
tablets as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in 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 was favourable, and therefore recommended the granting of the Marketing Authorisations.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is fully completed and that the PDCO issued an Opinion on Compliance. The CHMP reviewed the paediatric data of studies subject to this plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications has been judged to be satisfactory.

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

EFFICACY
The supporting studies have shown that the finished product is efficacious in the target population. The level of adverse events was considered comparable to the already marketed atorvastatin containing products.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new pre-clinical or clinical safety concerns have been identified. Extensive clinical experience with atorvastatin is considered to have demonstrated the therapeutic value of the compounds. The risk:benefit is, therefore, considered to be positive.
# LIPITOR 5MG, 10MG, 20MG AND 40MG CHEWABLE TABLETS

**PL 16051/0006-9**

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## STEPS TAKEN FOR ASSESSMENT

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<thead>
<tr>
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<td>1</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 4th August 2010.</td>
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<td>5</td>
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LIPITOR 5MG, 10MG, 20MG AND 40MG CHEWABLE TABLETS
PL 16051/0006-9

STEPS TAKEN AFTER ASSESSMENT

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<th>Application type</th>
<th>Scope</th>
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**SUMMARY OF PRODUCT CHARACTERISTICS**

1 **NAME OF THE MEDICINAL PRODUCT**
   Lipitor™ 5mg chewable tablets.

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
   Each chewable tablet contains 5mg atorvastatin as atorvastatin calcium trihydrate.
   Each Lipitor 5 mg chewable tablet contains 0.625 mg aspartame.
   For excipients see section 6.1.

3 **PHARMACEUTICAL FORM**
   Chewable tablet.
   White to off-white, round chewable tablets with pink to purple specks, debossed "5" on one side and “Pfizer” on the other measuring 5.6 mm in diameter.

4 **CLINICAL PARTICULARS**
4.1 **THERAPEUTIC INDICATIONS**

   **Hypercholesterolaemia:**
   Lipitor is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

   Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

   Lipitor is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in adults with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

   **Primary prevention in type II diabetes:**
   Lipitor is indicated for reducing the risk of cardiovascular events in diabetic patients with at least 1 additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol is raised. See section 5.1.

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

   For patients taking interacting drugs that increase plasma exposure to atorvastatin, the starting dose should be 10 mg once a day, and a maximum dose of less than 80mg may need to be considered. In some cases a dose reduction, or where not practical, a temporary dose suspension may be considered (see Sections 4.4 and 4.5).

   Doses above 20mg/day have not been investigated in patients aged <18 years. Doses may be given at any time of day with or without food.

   **Adult use**
   **Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia**
   **Adults:**
   The majority of patients are controlled with 10 mg Lipitor once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

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

   **Heterozygous Familial Hypercholesterolaemia**
   **Adults:**
Patients should be started with Lipitor 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg, colestipol) may be combined with 40 mg Lipitor.

Homozygous Familial Hypercholesterolaemia
Adults: In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Lipitor (see Section 5.1 Pharmacodynamics).

Dosage in Patients With Renal Insufficiency
Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required (see section 4.4 Special warnings and precautions for use).

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

Geriatric Use
Adequate treatment experience in adults age 70 or older with doses of Lipitor up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

Prevention of Cardiovascular disease
In the primary prevention trials, the dose was 10mg/day (see section 5.1 for the lipid levels where this dose was found to be effective, patients with higher levels will require conventional measurement and dose titration).

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.

Lipitor tablets can be chewed or swallowed whole with a drink of water, and can be taken at any time of day, with or without food.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Liver Effects
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 ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended.

Lipitor should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
**Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)**

In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or TIA there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Section 5.1).

**Muscle effects**

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

**Creatine phosphokinase measurement**

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

**Before treatment**

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

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

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

**Whilst on treatment**

- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated (>5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Risk of dose-related side effects including rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates or HIV-protease inhibitors. The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-
administration of these medications with atorvastatin is only necessary for a few days, a dose reduction or where not practical, a temporary suspension of treatment with atorvastatin may be considered. If co-administration with interacting drugs is unavoidable, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see Section 4.5). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is employed.

Lipitor chewable tablet contains aspartame which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (see Section 4.5)

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals, HIV-protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and Section 4.2). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used. (see Section 4.4).

Transporter Inhibitors:
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an 8.7 fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg.

Clarithromycin: Clarithromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 80 mg OD and clarithromycin (500 mg BID) resulted in a 4.4 fold increase in atorvastatin AUC. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

Erythromycin: Erythromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID) resulted in a 33% increase in exposure to total atorvastatin activity.

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

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

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

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

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

**Grapefruit juice**: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

**Inducers of cytochrome P450 3A4**: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

**Verapamil and Amiodarone**: Interaction studies with atorvastatin and verapamil or amiodarone have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

**Other concomitant therapy**

**Gemfibrozil/fibrates**: The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see Section 4.4). Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in atorvastatin AUC.

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

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

**Colestipol**: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with Lipitor. However, lipid effects were greater when Lipitor and colestipol were administered together than when either drug was given alone.

**Antacid**: Administration of Lipitor with an oral antacid suspension containing magnesium and aluminum hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.
**Warfarin:** Administration of Lipitor with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg Lipitor. Dosing continued for 15 days and prothrombin time returned to normal by the end of Lipitor treatment. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.

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

**Cimetidine:** An interaction study with cimetidine and Lipitor was conducted, and no interaction was seen.

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

**Fusidic acid:** Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

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

**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 PREGNANCY AND LACTATION
Lipitor is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

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

In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal 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 atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

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

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

### 4.8 UNDESIRABLE EFFECTS
Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

The most frequent (1% or more) adverse effects that may be associated with Lipitor therapy, reported in patients participating in controlled clinical studies include:

**Infections and infestations:** nasopharyngitis

**Metabolism and nutrition disorders:** hyperglycemia
**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain, epistaxis

**Gastrointestinal disorders:** abdominal pain, constipation, diarrhoea, dyspepsia, nausea, flatulence

**Musculoskeletal and connective tissue disorders:** arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling

**Investigations:** liver function test abnormal, blood creatine phosphokinase increased

**Psychiatric Disorders:** insomnia

**Nervous System Disorders:** headache

**General Disorders and Administration Site Conditions:** asthenia

Elevated serum ALT levels have been reported in 1.3% of patients receiving Lipitor. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in 19 of the 2483 (0.8%) patients on Lipitor. It was dose related and was reversible in all 19 patients. In 10 cases, the increase was first observed within 12 weeks of starting the treatment. Only 1 case occurred after 36 weeks and only 1 patient had symptoms suggestive of hepatitis. Treatment was discontinued in only 9 of these 19 cases.

Elevated serum CPK levels (>3 times upper normal limit) occurred in 62 of the 2452 (2.5%) patients on Lipitor compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 11 (0.4%) Lipitor-treated patients. Only 3 (0.1%) of these 11 patients had concurrent muscle pain, tenderness, or weakness.

Adverse events reported in atorvastatin clinical trials and in post marketing experience are categorised below according to system organ class and frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%) and very rare (<0.01%).

**Gastrointestinal disorders**
- Common: constipation, flatulence, dyspepsia, nausea, diarrhoea
- Uncommon: anorexia, vomiting, pancreatitis, abdominal discomfort
- Rare: eructation

**Blood and lymphatic system disorders**
- Uncommon: thrombocytopenia.

**Immune system disorders**
- Common: allergic reactions (including anaphylaxis).

**Endocrine disorders**
- Uncommon: alopecia, hyperglycaemia, hypoglycaemia.

**Psychiatric**
- Common: insomnia.
- Uncommon: amnesia, nightmare.

**Nervous system disorders**
- Common: headache, dizziness, paraesthesia, hypoesthesia.
- Uncommon: peripheral neuropathy.
- Very rare: dysgeusia.

**Eye disorders**
- Uncommon: vision blurred
- Very rare: visual disturbance.
Hepato-biliary disorders
Rare: hepatitis, cholestasis.
Very rare: hepatic failure.

Skin/Appendages
Common: Skin rash, pruritus
Uncommon: urticaria, alopecia.
Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Ear and Labyrinth Disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Musculoskeletal disorders
Common: myalgia, arthralgia.
Uncommon: myopathy, muscle cramps, neck pain.
Rare: myositis, rhabdomyolysis, muscle fatigue.
Very rare: tendon rupture.

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

General disorders
Common: asthenia, chest pain, back pain, fatigue.
Uncommon: malaise, weight gain.
Rare: peripheral oedema, pyrexia

Investigations
Rare: white blood cells urine positive
The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares.
- Memory loss.
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see Section 4.4).

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

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites (see Section 5.2 Pharmacokinetic Properties).

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides while producing variable increases in HDL-C in a dose-response study as shown in Table 1 below.

<table>
<thead>
<tr>
<th>Lipitor Dose (mg)</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>ApoB</th>
<th>TG</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>-30</td>
<td>-41</td>
<td>-34</td>
<td>-14</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>-35</td>
<td>-44</td>
<td>-36</td>
<td>-33</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>11</td>
<td>-38</td>
<td>-50</td>
<td>-41</td>
<td>-25</td>
<td>-3</td>
</tr>
<tr>
<td>80</td>
<td>11</td>
<td>-46</td>
<td>-61</td>
<td>-50</td>
<td>-27</td>
<td>3</td>
</tr>
</tbody>
</table>

Adjusted Mean % Change from Baseline

Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

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

Lipitor is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication. In a compassionate use study, 41 patients aged 6 to 51 years with homozygous familial hypercholesterolaemia or with severe hypercholesterolaemia, who had ≤15% reduction in LDL-C in response to previous maximum dose combination drug therapy, received daily doses of 40 to 80 mg of Lipitor. Twenty four patients with homozygous familial hypercholesterolaemia received 80 mg Lipitor. Nineteen of these 24 patients responded with a greater than 15% reduction of LDL-C (mean 26%, range 18% to 42%).

Atherosclerosis

11. In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis evaluated by the percentage change in atheroma volume in a pre-defined target vessel with a stenosis
between 20% and 50%. 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).

12. 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).

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

The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity was not investigated in this 18-month study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

**Prevention of Cardiovascular Disease**

In the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 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). Additionally, all patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL ≥ 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria.

In this randomised, double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy and either atorvastatin 10mg daily (n=5168) or placebo (n=5137). After 3 years treatment with amlodipine or atenolol-based regimen, mean blood pressure fell from 164.2/94.9 to 138.9/80.1 mmHg (atorvastatin) and 164.2/94.3 to 138.9/80.0 mmHg (placebo).

After a median of 3.3 years of treatment, there was a statistically significant reduction in the rate of myocardial infarction (a component of the primary endpoint), 1.2% on atorvastatin versus 2.1% on placebo.

Fatal and non-fatal ischaemic strokes tended to be lower in the atorvastatin group with a relative risk reduction of 26% (89 vs. 119 events) and an absolute risk reduction of 0.6%. The difference did not reach pre-defined levels of statistical significance.

Women constituted 20% of the trial population and a subgroup analysis did not demonstrate any benefit on the primary endpoint of coronary events (fatal CHD plus non-fatal MI) (RR 1.11, 95% CI 0.58-2.13).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78 mmol/l (600 mg/dl). Additionally, all patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomised, double-blind, multi-centre, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction (%)</th>
<th>No of events (atorvastatin vs.placebo)</th>
<th>p-value</th>
</tr>
</thead>
</table>

51
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)  

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Risk 1</th>
<th>Risk 2</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>1.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>1.3%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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.

Although the relative risk reduction in the primary end-point was similar between men and women, the absolute benefit for the women was less since the primary event rate on placebo was approximately 1/3 of the male event rate.

Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dl (3.4 mmol/l). The mean LDL-C was 73 mg/dl (1.9 mmol/l) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

- The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

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

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

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

#### Pharmacokinetics and Drug Metabolism

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

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

**Metabolism:** Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. 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 and atorvastatin metabolites are substrates of P-glycoprotein (see section 4.5). Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special Populations**
Geriatric: Plasma concentrations of atorvastatin 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 in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 PRECLINICAL SAFETY DATA
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16-fold higher based on AUC(0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC(0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Calcium carbonate
Microcrystalline cellulose
Croscarmellose sodium
Polysorbate 80
Magnesium stearate
Hydroxypropyl cellulose
Amylum pregelificatum
Mannitol (E421)
Aspartame (E951)
Sucralose (E955)
Grape flavour

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
No special precautions for storage.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister packs containing 30 chewable tablets.
The blisters consist of a forming foil made of polyamide/aluminium foil/polyvinyl chloride and a backing made of aluminium foil/vinyl/acryl heat-seal coating.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
This medicinal product does not require any special storage conditions.

7 MARKETING AUTHORISATION HOLDER
Pfizer Ireland Pharmaceuticals
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

8 MARKETING AUTHORIZATON NUMBER(S)
PL 16051/0006

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
03/11/2010

10 DATE OF REVISION OF THE TEXT
03/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Lipitor™ 10mg chewable tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each chewable tablet contains 10mg atorvastatin as atorvastatin calcium trihydrate.
Each Lipitor 10 mg chewable tablet contains 1.25 mg aspartame.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM
Chewable tablet.
White to off-white, round chewable tablets with pink to purple specks, debossed “10” on one side and “Pfizer” on the other measuring 7.1 mm in diameter.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
**Hypercholesterolaemia:**
Lipitor is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Lipitor is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in adults with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

**Primary prevention in type II diabetes:**
Lipitor is indicated for reducing the risk of cardiovascular events in diabetic patients with at least 1 additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol is raised. See section 5.1.

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

For patients taking interacting drugs that increase plasma exposure to atorvastatin, the starting dose should be 10 mg once a day, and a maximum dose of less than 80mg may need to be considered. In some cases a dose reduction, or where not practical, a temporary dose suspension may be considered (see Sections 4.4 and 4.5).

Doses above 20mg/day have not been investigated in patients aged <18 years. Doses may be given at any time of day with or without food.

**Adult use**
**Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia**

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

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

**Heterozygous Familial Hypercholesterolaemia**

**Adults:**
Patients should be started with Lipitor 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg, colestipol) may be combined with 40 mg Lipitor.

**Homozogous Familial Hypercholesterolaemia**

**Adults:** In a compassionate-use study of patients with homozogous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Lipitor (see Section 5.1 Pharmacodynamics).

**Dosage in Patients With Renal Insufficiency**

Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required (see section 4.4 Special warnings and precautions for use).

**Dosage in Patients With Hepatic Dysfunction**

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

**Geriatric Use**

Adequate treatment experience in adults age 70 or older with doses of Lipitor up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

**Prevention of Cardiovascular disease**

In the primary prevention trials, the dose was 10mg/day (see section 5.1 for the lipid levels where this dose was found to be effective, patients with higher levels will require conventional measurement and dose titration).

**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.

Lipitor tablets can be chewed or swallowed whole with a drink of water, and can be taken at any time of day, with or without food.

4.3 **CONTRAINDICATIONS**

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

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**Liver Effects**

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 ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended.

Lipitor should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or TIA there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Section 5.1).

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

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

Before treatment
As with other statins atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

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

Whilst on treatment
- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤ 5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Risk of dose-related side effects including rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates or HIV-protease inhibitors. The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-
administration of these medications with atorvastatin is only necessary for a few days, a dose reduction or where not practical, a temporary suspension of treatment with atorvastatin may be considered. If co-administration with interacting drugs is unavoidable, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see Section 4.5). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is employed.

Lipitor chewable tablet contains aspartame which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (see Section 4.5)

**Interstitial lung disease**
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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

### 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals, HIV- protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and Section 4.2). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used. (see Section 4.4).

**Transporter Inhibitors:**
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an 8.7 fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg.

**Clarithromycin:** Clarithromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 80 mg OD and clarithromycin (500 mg BID) resulted in a 4.4 fold increase in atorvastatin AUC. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

**Erythromycin:** Erythromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID) resulted in a 33% increase in exposure to total atorvastatin activity.

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

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

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

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

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

**Grapefruit juice:** Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

**Inducers of cytochrome P450 3A4:** Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

**Verapamil and Amiodarone:** Interaction studies with atorvastatin and verapamil or amiodarone have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

**Other concomitant therapy**

**Gemfibrozil/fibrates:** The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see Section 4.4). Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in atorvastatin AUC.

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

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

**Colestipol:** Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with Lipitor. However, lipid effects were greater when Lipitor and colestipol were administered together than when either drug was given alone.

**Antacid:** Administration of Lipitor with an oral antacid suspension containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.
**Warfarin:** Administration of Lipitor with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg Lipitor. Dosing continued for 15 days and prothrombin time returned to normal by the end of Lipitor treatment. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.

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

**Cimetidine:** An interaction study with cimetidine and Lipitor was conducted, and no interaction was seen.

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

**Fusidic acid:** Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

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

**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 PREGNANCY AND LACTATION**
Lipitor is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

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

In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal 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 atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

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

**4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

**4.8 UNDESIRABLE EFFECTS**
Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

The most frequent (1% or more) adverse effects that may be associated with Lipitor therapy, reported in patients participating in controlled clinical studies include:

**Infections and infestations:** nasopharyngitis

**Metabolism and nutrition disorders:** hyperglycemia
**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain, epistaxis

**Gastrointestinal disorders:** abdominal pain, constipation, diarrhoea, dyspepsia, nausea, flatulence

**Musculoskeletal and connective tissue disorders:** arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling

**Investigations:** liver function test abnormal, blood creatine phosphokinase increased

**Psychiatric Disorders:** insomnia

**Nervous System Disorders:** headache

**General Disorders and Administration Site Conditions:** asthenia

Elevated serum ALT levels have been reported in 1.3% of patients receiving Lipitor. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in 19 of the 2483 (0.8%) patients on Lipitor. It was dose related and was reversible in all 19 patients. In 10 cases, the increase was first observed within 12 weeks of starting the treatment. Only 1 case occurred after 36 weeks and only 1 patient had symptoms suggestive of hepatitis. Treatment was discontinued in only 9 of these 19 cases.

Elevated serum CPK levels (>3 times upper normal limit) occurred in 62 of the 2452 (2.5%) patients on Lipitor compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 11 (0.4%) Lipitor-treated patients. Only 3 (0.1%) of these 11 patients had concurrent muscle pain, tenderness, or weakness.

Adverse events reported in atorvastatin clinical trials and in post marketing experience are categorised below according to system organ class and frequency. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%) and very rare (<0.01%).

**Gastrointestinal disorders**
- Common: constipation, flatulence, dyspepsia, nausea, diarrhoea
- Uncommon: anorexia, vomiting, pancreatitis, abdominal discomfort
- Rare: eructation

**Blood and lymphatic system disorders**
- Uncommon: thrombocytopenia.

**Immune system disorders**
- Common: allergic reactions (including anaphylaxis).

**Endocrine disorders**
- Uncommon: alopecia, hyperglycaemia, hypoglycaemia.

**Psychiatric**
- Common: insomnia.
- Uncommon: amnesia, nightmare.

**Nervous system disorders**
- Common: headache, dizziness, paraesthesia, hypoesthesia.
- Uncommon: peripheral neuropathy.
- Very rare: dysgeusia.

**Eye disorders**
- Uncommon: vision blurred
- Very rare: visual disturbance.
Hepato-biliary disorders
Rare: hepatitis, cholestasis.
Very rare: hepatic failure.

Skin/Appendages
Common: Skin rash, pruritus
Uncommon: urticaria, alopecia.
Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Ear and Labyrinth Disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Musculoskeletal disorders
Common: myalgia, arthralgia.
Uncommon: myopathy, muscle cramps, neck pain.
Rare: myositis, rhabdomyolysis, muscle fatigue.
Very rare: tendon rupture.

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

General disorders
Common: asthenia, chest pain, back pain, fatigue.
Uncommon: malaise, weight gain.
Rare: peripheral oedema, pyrexia

Investigations
Rare: white blood cells urine positive

The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares.
- Memory loss.
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see Section 4.4).

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

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites (see Section 5.2 Pharmacokinetic Properties).

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides while producing variable increases in HDL-C in a dose-response study as shown in Table 1 below.

<table>
<thead>
<tr>
<th>Lipitor Dose (mg)</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>TG</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>-30</td>
<td>-41</td>
<td>-34</td>
<td>-14</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>-35</td>
<td>-44</td>
<td>-36</td>
<td>-33</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>11</td>
<td>-38</td>
<td>-50</td>
<td>-41</td>
<td>-25</td>
<td>-3</td>
</tr>
<tr>
<td>80</td>
<td>11</td>
<td>-46</td>
<td>-61</td>
<td>-50</td>
<td>-27</td>
<td>3</td>
</tr>
</tbody>
</table>

Adjusted Mean % Change from Baseline

Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

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

Lipitor is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication. In a compassionate use study, 41 patients aged 6 to 51 years with homozygous familial hypercholesterolaemia or with severe hypercholesterolaemia, who had ≤15% reduction in LDL-C in response to previous maximum dose combination drug therapy, received daily doses of 40 to 80 mg of Lipitor. Twenty four patients with homozygous familial hypercholesterolaemia received 80 mg Lipitor. Nineteen of these 24 patients responded with a greater than 15% reduction of LDL-C (mean 26%, range 18% to 42%).

Atherosclerosis

11. In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis evaluated by the percentage change in atheroma volume in a pre-defined target vessel with a stenosis
between 20% and 50%. 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).

12. 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).

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

The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity was not investigated in this 18-month study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

Prevention of Cardiovascular Disease

In the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5mmol/l (251 mg/dl). Additionally, all patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL ≥ 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria.

In this randomised, double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy and either atorvastatin 10mg daily (n=5168) or placebo (n=5137). After 3 years treatment with amlodipine or atenolol-based regimen, mean blood pressure fell from 164.2/94.9 to 138.9/80.1 mmHg (atorvastatin) and 164.2/94.3 to 138.9/80.0 mmHg (placebo).

After a median of 3.3 years of treatment, there was a statistically significant reduction in the rate of myocardial infarction (a component of the primary endpoint), 1.2% on atorvastatin versus 2.1% on placebo.

Fatal and non-fatal ischaemic strokes tended to be lower in the atorvastatin group with a relative risk reduction of 26% (89 vs. 119 events) and an absolute risk reduction of 0.6%. The difference did not reach pre-defined levels of statistical significance.

Women constituted 20% of the trial population and a subgroup analysis did not demonstrate any benefit on the primary endpoint of coronary events (fatal CHD plus non-fatal MI) (RR 1.11, 95% CI 0.58-2.13).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78mmol/l (600mg/dl). Additionally, all patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomised, double-blind, multi-centre, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction (%)</th>
<th>No of events (atorvastatin vs.placebo)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)  
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Event Rate</th>
<th>Placebo Rate</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>1.9%</td>
<td>.007</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>1.3%</td>
<td>.016</td>
</tr>
</tbody>
</table>

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.

Although the relative risk reduction in the primary end-point was similar between men and women, the absolute benefit for the women was less since the primary event rate on placebo was approximately 1/3 of the male event rate.

Recurrent Stroke

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dL (3.4 mmol/l). The mean LDL-C was 73 mg/dl (1.9 mmol/l) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

- The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

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

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

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 $>3.36 \text{ mmol/l}$. 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

**Pharmacokinetics and Drug Metabolism**

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

**Distribution:** Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is $\geq98\%$ bound to plasma proteins.

**Metabolism:** Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. 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 and atorvastatin metabolites are substrates of P-glycoprotein (see section 4.5). Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special Populations**
Geriatric: Plasma concentrations of atorvastatin 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 in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 PRECLINICAL SAFETY DATA
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16-fold higher based on AUC(0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC(0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Calcium carbonate
Microcrystalline cellulose
Croscarmellose sodium
Polysorbate 80
Magnesium stearate
Hydroxypropyl cellulose
Amylum pregelificatum
Mannitol (E421)
Aspartame (E951)
Sucralose (E955)
Grape flavour

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister packs containing 30 chewable tablets.
The blisters consist of a forming foil made of polyamide/aluminium foil/polyvinyl chloride and a backing made of aluminium foil/vinyl/acryl heat-seal coating.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7 MARKETING AUTHORISATION HOLDER
Pfizer Ireland Pharmaceuticals
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16051/0007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2010

10 DATE OF REVISION OF THE TEXT
03/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Lipitor™ 20mg chewable tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each chewable tablet contains 20mg atorvastatin as atorvastatin calcium trihydrate.
Each Lipitor 20 mg chewable tablet contains 2.5 mg aspartame.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM
Chewable tablet.
White to off-white, round chewable tablets with pink to purple specks debossed "20" on one side and "Pfizer" on the other measuring 8.7 mm in diameter.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

Hypercholesterolaemia:
Lipitor is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidemia when response to diet and other nonpharmacological measures is inadequate.

Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Lipitor is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in adults with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

Primary prevention in type II diabetes:
Lipitor is indicated for reducing the risk of cardiovascular events in diabetic patients with at least 1 additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol is raised. See section 5.1.

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

For patients taking interacting drugs that increase plasma exposure to atorvastatin, the starting dose should be 10 mg once a day, and a maximum dose of less than 80mg may need to be considered. In some cases a dose reduction, or where not practical, a temporary dose suspension may be considered (see Sections 4.4 and 4.5).

Doses above 20mg/day have not been investigated in patients aged <18 years. Doses may be given at any time of day with or without food.

Adult use

Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

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

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

Heterozygous Familial Hypercholesterolaemia

Adults:
Patients should be started with Lipitor 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg, colestipol) may be combined with 40 mg Lipitor.

**Homozgyous Familial Hypercholesterolaemia**

*Adults:* In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Lipitor (see Section 5.1 Pharmacodynamics).

**Dosage in Patients With Renal Insufficiency**

Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required (see section 4.4 Special warnings and precautions for use).

**Dosage in Patients With Hepatic Dysfunction**

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

**Geriatric Use**

Adequate treatment experience in adults age 70 or older with doses of Lipitor up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

**Prevention of Cardiovascular disease**

In the primary prevention trials, the dose was 10mg/day (see section 5.1 for the lipid levels where this dose was found to be effective, patients with higher levels will require conventional measurement and dose titration).

**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.

Lipitor tablets can be chewed or swallowed whole with a drink of water, and can be taken at any time of day, with or without food.

4.3 **CONTRAINDICATIONS**

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

4.4 **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**Liver Effects**

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 ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended.

Lipitor should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or TIA there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Section 5.1).

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

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

Before treatment
As with other statins atorvastatin should be prescribed with caution in patients with pre-disposing factors for rhabdomyolysis. A creatine phosphokinase (CPK) level should be measured before starting treatment in the following situations:
- Renal impairment
- Hypothyroidism
- Personal or familial history of hereditary muscular disorders
- Previous history of muscular toxicity with a statin or fibrate
- Previous history of liver disease and/or where substantial quantities of alcohol are consumed
- In elderly (age > 70 years), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis

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

Whilst on treatment
- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated (>5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Risk of dose-related side effects including rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates or HIV-protease inhibitors. The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-
administration of these medications with atorvastatin is only necessary for a few days, a dose reduction or where not practical, a temporary suspension of treatment with atorvastatin may be considered. If co-administration with interacting drugs is unavoidable, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see Section 4.5). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is employed.

Lipitor chewable tablet contains aspartame which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (see Section 4.5)

Interstitial lung disease
Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals, HIV-protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and Section 4.2). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used. (see Section 4.4).

Transporter Inhibitors:
Atorvastatin and atorvastatin-metabolites are substrates of the OATP1B1 transporter. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an 8.7 fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg.

Clarithromycin: Clarithromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 80 mg OD and clarithromycin (500 mg BID) resulted in a 4.4 fold increase in atorvastatin AUC. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

Erythromycin: Erythromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID) resulted in a 33% increase in exposure to total atorvastatin activity.

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

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

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

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

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

**Grapefruit juice:** Contains one or more components that inhibit CYP3A4 and can increase plasma
conzentations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice
resulted in an increase in atorvastatin AUC of 37 % and a decreased AUC of 20.4 % for the active
orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days)
increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA
reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and
atorvastatin is therefore not recommended.

**Inducers of cytochrome P450 3A4:** Concomitant administration of atorvastatin with inducers of
cytochrome P450 3A4 (eg efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in
plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin,
(cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1),
simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed
administration of atorvastatin after administration of rifampin has been associated with a significant
reduction in atorvastatin plasma concentrations.

**Verapamil and Amiodarone:** Interaction studies with atorvastatin and verapamil or amiodarone
have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity
and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels
should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

**Other concomitant therapy**

**Gemfibrozil/fibrates:** The use of fibrates alone is occasionally associated with myopathy. The risk
of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see
Section 4.4). Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in
atorvastatin AUC.

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

**Oral contraceptives:** Administration of Lipitor with an oral contraceptive containing norethisterone
and ethiny1 oestradiol produced increases in plasma concentrations of norethisterone and ethiny1
oestradiol. These increased concentrations should be considered when selecting oral contraceptive
doses.

**Colestipol:** Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol
was administered with Lipitor. However, lipid effects were greater when Lipitor and colestipol were
administered together than when either drug was given alone.

**Antacid:** Administration of Lipitor with an oral antacid suspension containing magnesium and
aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however,
LDL-C reduction was not altered.
Warfarin: Administration of Lipitor with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg Lipitor. Dosing continued for 15 days and prothrombin time returned to normal by the end of Lipitor treatment. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.

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

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

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

Fusidic acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

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

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 PREGNANCY AND LACTATION
Lipitor is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

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

In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal 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 atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

4.8 UNDESIRABLE EFFECTS
Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

The most frequent (1% or more) adverse effects that may be associated with Lipitor therapy, reported in patients participating in controlled clinical studies include:

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: hyperglycemia
**Respiratory, thoracic and mediastinal disorders:** pharyngolaryngeal pain, epistaxis

**Gastrointestinal disorders:** abdominal pain, constipation, diarrhoea, dyspepsia, nausea, flatulence

**Musculoskeletal and connective tissue disorders:** arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling

**Investigations:** liver function test abnormal, blood creatine phosphokinase increased

**Psychiatric Disorders:** insomnia

**Nervous System Disorders:** headache

**General Disorders and Administration Site Conditions:** asthenia

Elevated serum ALT levels have been reported in 1.3% of patients receiving Lipitor. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in 19 of the 2483 (0.8%) patients on Lipitor. It was dose related and was reversible in all 19 patients. In 10 cases, the increase was first observed within 12 weeks of starting the treatment. Only 1 case occurred after 36 weeks and only 1 patient had symptoms suggestive of hepatitis. Treatment was discontinued in only 9 of these 19 cases.

Elevated serum CPK levels (>3 times upper normal limit) occurred in 62 of the 2452 (2.5%) patients on Lipitor compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 11 (0.4%) Lipitor-treated patients. Only 3 (0.1%) of these 11 patients had concurrent muscle pain, tenderness, or weakness.

Adverse events reported in atorvastatin clinical trials and in post marketing experience are categorised below according to system organ class and frequency. Frequencies are defined as: very common (>10%), common (>1% and <10%), uncommon (>0.1% and <1%), rare (>0.01% and <0.1%) and very rare (<0.01%).

**Gastrointestinal disorders**
- Common: constipation, flatulence, dyspepsia, nausea, diarrhoea
- Uncommon: anorexia, vomiting, pancreatitis, abdominal discomfort
- Rare: eructation

**Blood and lymphatic system disorders**
- Uncommon: thrombocytopenia.

**Immune system disorders**
- Common: allergic reactions (including anaphylaxis).

**Endocrine disorders**
- Uncommon: alopecia, hyperglycaemia, hypoglycaemia.

**Psychiatric**
- Common: insomnia.
- Uncommon: amnesia, nightmare.

**Nervous system disorders**
- Common: headache, dizziness, paraesthesia, hypoesthesia.
- Uncommon: peripheral neuropathy.
- Very rare: dysgeusia.

**Eye disorders**
- Uncommon: vision blurred
- Very rare: visual disturbance.
Hepato-biliary disorders
Rare: hepatitis, cholestasis.
Very rare: hepatic failure.

Skin/Appendages
Common: Skin rash, pruritus
Uncommon: urticaria, alopecia.
Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Ear and Labyrinth Disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Musculoskeletal disorders
Common: myalgia, arthralgia.
Uncommon: myopathy, muscle cramps, neck pain.
Rare: myositis, rhabdomyolysis, muscle fatigue.
Very rare: tendon rupture.

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

General disorders
Common: asthenia, chest pain, back pain, fatigue.
Uncommon: malaise, weight gain.
Rare: peripheral oedema, pyrexia

Investigations
Rare: white blood cells urine positive
The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares.
- Memory loss.
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see Section 4.4).

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

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

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

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

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites (see Section 5.2 Pharmacokinetic Properties).

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides while producing variable increases in HDL-C in a dose-response study as shown in Table 1 below.

TABLE 1. Dose Response in Patients with Primary Hypercholesterolaemia

<table>
<thead>
<tr>
<th>Lipitor Dose (mg)</th>
<th>N</th>
<th>Total C</th>
<th>LDL C</th>
<th>Apo B</th>
<th>TG</th>
<th>HDL C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
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<td>5</td>
<td>8</td>
<td>6</td>
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<td>-3</td>
</tr>
<tr>
<td>80</td>
<td>11</td>
<td>-46</td>
<td>-61</td>
<td>-50</td>
<td>-27</td>
<td>3</td>
</tr>
</tbody>
</table>

Adjusted Mean % Change from Baseline

Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

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

Lipitor is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication. In a compassionate use study, 41 patients aged 6 to 51 years with homozygous familial hypercholesterolaemia or with severe hypercholesterolaemia, who had ≤15% reduction in LDL-C in response to previous maximum dose combination drug therapy, received daily doses of 40 to 80 mg of Lipitor. Twenty four patients with homozygous familial hypercholesterolaemia received 80 mg Lipitor. Nineteen of these 24 patients responded with a greater than 15% reduction of LDL-C (mean 26%, range 18% to 42%).

**Atherosclerosis**

11. In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis evaluated by the percentage change in atheroma volume in a pre-defined target vessel with a stenosis
between 20% and 50%. 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).

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).

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

The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity was not investigated in this 18-month study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

**Prevention of Cardiovascular Disease**

In the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5mmol/l (251 mg/dl). Additionally, all patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL ≥ 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria.

In this randomised, double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy and either atorvastatin 10mg daily (n=5168) or placebo (n=5137). After 3 years treatment with amlodipine or atenolol-based regimen, mean blood pressure fell from 164.2/94.9 to 138.9/80.1 mmHg (atorvastatin) and 164.2/94.3 to 138.9/80.0 mmHg (placebo).

After a median of 3.3 years of treatment, there was a statistically significant reduction in the rate of myocardial infarction (a component of the primary endpoint), 1.2% on atorvastatin versus 2.1% on placebo.

Fatal and non-fatal ischaemic strokes tended to be lower in the atorvastatin group with a relative risk reduction of 26% (89 vs. 119 events) and an absolute risk reduction of 0.6%. The difference did not reach pre-defined levels of statistical significance.

Women constituted 20% of the trial population and a subgroup analysis did not demonstrate any benefit on the primary endpoint of coronary events (fatal CHD plus non-fatal MI) (RR 1.11, 95% CI 0.58-2.13).

In the Collaborative Atorvastatin Diabetes Study (CADS), the effect of atorvastatin on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78mmol/l (600mg/dl). Additionally, all patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomised, double-blind, multi-centre, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction (%)</th>
<th>No of events (atorvastatin vs.placebo)</th>
<th>p-value</th>
</tr>
</thead>
</table>

\[ \text{Relative Risk Reduction} = \frac{\text{Risk in placebo group} - \text{Risk in atorvastatin group}}{\text{Risk in placebo group}} \times 100 \]

\[ \text{Absolute Risk Reduction} = \text{Risk in placebo group} - \text{Risk in atorvastatin group} \]

\[ \text{No of events} = \text{Number of events in placebo group} - \text{Number of events in atorvastatin group} \]
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CAGB, PTCA, revascularisation, stroke)  

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Lipitor 5mg (%)</th>
<th>Lipitor 10mg (%)</th>
<th>Lipitor 20mg (%)</th>
<th>Lipitor 40mg (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>1.9%</td>
<td>38 vs. 64</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>1.3%</td>
<td>21 vs. 39</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

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

Although the relative risk reduction in the primary end-point was similar between men and women, the absolute benefit for the women was less since the primary event rate on placebo was approximately 1/3 of the male event rate.

Recurrent Stroke
In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, the effect of atorvastatin 80 mg daily or placebo on stroke was evaluated in 4731 patients who had a stroke or transient ischemic attack (TIA) within the preceding 6 months and no history of coronary heart disease (CHD). Patients were 60% male, 21-92 years of age (average age 63 years) and had an average baseline LDL of 133 mg/dl (3.4 mmol/l). The mean LDL-C was 73 mg/dl (1.9 mmol/l) during treatment with atorvastatin and 129 mg/dL (3.3 mmol/L) during treatment with placebo. Median follow-up was 4.9 years.

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

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

- The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 0.84-19.57) and the risk of ischemic stroke was similar between groups (3/45 for atorvastatin versus 2/48 for placebo; HR 1.64; 95% CI, 0.27-9.82).

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

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

**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

**Pharmacokinetics and Drug Metabolism**

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

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

**Metabolism:** Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. 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 and atorvastatin metabolites are substrates of P-glycoprotein (see section 4.5). Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special Populations**
Geriatric: Plasma concentrations of atorvastatin 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 in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 PRECLINICAL SAFETY DATA
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16-fold higher based on AUC(0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC(0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Calcium carbonate
Microcrystalline cellulose
Croscarmellose sodium
Polysorbate 80
Magnesium stearate
Hydroxypropyl cellulose
Amylum pregelificatum
Mannitol (E421)
Aspartame (E951)
Sucralose (E955)
Grape flavour

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters containing 30 chewable tablets. The blisters consist of a forming foil made of polyamide/aluminium foil/polyvinyl chloride and a backing made of aluminium foil/vinyl/acryl heat-seal coating.
6.6  SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7  MARKETING AUTHORISATION HOLDER
Pfizer Ireland Pharmaceuticals
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

8  MARKETING AUTHORISATION NUMBER(S)
PL 16051/0008

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2010

10  DATE OF REVISION OF THE TEXT
03/11/2010
1 NAME OF THE MEDICINAL PRODUCT
Lipitor™ 40mg chewable tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each chewable tablet contains 40mg atorvastatin as atorvastatin calcium trihydrate.
Each Lipitor 40 mg chewable tablet contains 5 mg aspartame.
For excipients see section 6.1.

3 PHARMACEUTICAL FORM
Chewable tablet.
White to off-white, round chewable tablets with pink to purple specks, debossed “40” on one side and "Pfizer" on the other measuring 10.3 mm in diameter.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS

Hypercholesterolaemia:
Lipitor is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older with primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia when response to diet and other nonpharmacological measures is inadequate.

Lipitor also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Lipitor is also indicated as an adjunct to diet and other non-dietary measures in reducing elevated total cholesterol, LDL-cholesterol, and apolipoprotein B in adults with homozygous familial hypercholesterolaemia when response to these measures is inadequate.

Primary prevention in type II diabetes:
Lipitor is indicated for reducing the risk of cardiovascular events in diabetic patients with at least 1 additional risk factor, without clinically evident coronary heart disease irrespective of whether cholesterol is raised. See section 5.1.

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

For patients taking interacting drugs that increase plasma exposure to atorvastatin, the starting dose should be 10 mg once a day, and a maximum dose of less than 80mg may need to be considered. In some cases a dose reduction, or where not practical, a temporary dose suspension may be considered (see Sections 4.4 and 4.5).

Doses above 20mg/day have not been investigated in patients aged <18 years. Doses may be given at any time of day with or without food.

Adult use
Primary Hypercholesterolaemia and Combined (Mixed) Hyperlipidaemia

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

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

Heterozygous Familial Hypercholesterolaemia

Adults:
Patients should be started with Lipitor 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant (eg, colestipol) may be combined with 40 mg Lipitor.

**Homozygous Familial Hypercholesterolaemia**

**Adults:** In a compassionate-use study of patients with homozygous familial hypercholesterolaemia, most patients responded to a dose of 80 mg of Lipitor (see Section 5.1 Pharmacodynamics).

**Dosage in Patients With Renal Insufficiency**

Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor; thus, no adjustment of dose is required (see section 4.4 Special warnings and precautions for use).

**Dosage in Patients With Hepatic Dysfunction**

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

**Geriatric Use**

Adequate treatment experience in adults age 70 or older with doses of Lipitor up to 80 mg/day has been obtained. Efficacy and safety in older patients using recommended doses is similar to that seen in the general population.

**Prevention of Cardiovascular disease**

In the primary prevention trials, the dose was 10mg/day (see section 5.1 for the lipid levels where this dose was found to be effective, patients with higher levels will require conventional measurement and dose titration).

**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.

Lipitor tablets can be chewed or swallowed whole with a drink of water, and can be taken at any time of day, with or without food.

**4.3 CONTRAINDICATIONS**

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

**4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

**Liver Effects**

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 ALT or AST of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of Lipitor is recommended.

Lipitor should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
In a post-hoc analysis of stroke subtypes in patients without CHD who had a recent stroke or TIA there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to placebo. The increased risk was particularly noted in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain and the potential risk of haemorrhagic stroke should be carefully considered before initiating treatment (see Section 5.1).

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

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

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

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

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

Whilst on treatment
- If muscular pain, weakness or cramps occur whilst a patient is receiving treatment with a statin, their CPK levels should be measured. If these levels are found to be significantly elevated (> 5 times ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if CPK levels are elevated to ≤5 times ULN, treatment discontinuation should be considered.
- If symptoms resolve and CPK levels return to normal, then re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.

These CPK elevations should be considered when evaluating the possibility of myocardial infarction in the differential diagnosis of chest pain.

As with other drugs in this class, rhabdomyolysis with acute renal failure has been reported. A history of renal impairment may be a risk factor for the development of rhabdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Risk of dose-related side effects including rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medications that may increase the plasma concentration of atorvastatin such as: ciclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other fibrates or HIV-protease inhibitors. The risk of myopathy may also be increased with the concomitant use of ezetimibe. If possible alternative (non-interacting) therapies should be considered instead of these medications. In cases where co-
administration of these medications with atorvastatin is only necessary for a few days, a dose reduction or where not practical, a temporary suspension of treatment with atorvastatin may be considered. If co-administration with interacting drugs is unavoidable, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see Section 4.5). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is employed.

Lipitor chewable tablet contains aspartame which is a source of phenylalanine. May be harmful for people with phenylketonuria.

Temporary suspension of atorvastatin may be appropriate during fusidic acid therapy (see Section 4.5)

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section 4.8). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Paediatric use

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

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibrates, macrolide antibiotics including erythromycin, azole antifungals, HIV-protease inhibitors or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. In cases where co-administration of these medications with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. When patients are receiving drugs that increase the plasma concentration of atorvastatin, the starting dose of atorvastatin should be 10 mg once a day. In the case of ciclosporin, clarithromycin and itraconazole, a lower maximum dose of atorvastatin should be used (see below and Section 4.2). Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used. (see Section 4.4).

Transporter Inhibitors:

Atorvastatin and atorvastatin metabolites are substrates of the OATP1B1 transporter. Concomitant administration of atorvastatin 10 mg and ciclosporin 5.2 mg/kg/day resulted in an 8.7 fold increase in atorvastatin AUC. In cases where co-administration of atorvastatin with ciclosporin is necessary, the dose of atorvastatin should not exceed 10 mg.

Clarithromycin: Clarithromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 80 mg OD and clarithromycin (500 mg BID) resulted in a 4.4 fold increase in atorvastatin AUC. In cases where co-administration of clarithromycin with atorvastatin is necessary, the maintenance dose of atorvastatin should not exceed 20 mg daily. Patients who normally require 40mg or 80mg of atorvastatin should either reduce their dosage during concomitant clarithromycin treatment, or alternatively (for short courses of this antibiotic) where not practical, a temporary suspension of treatment with atorvastatin may be considered.

Erythromycin: Erythromycin is a known inhibitor of cytochrome P450 3A4. Co-administration of atorvastatin 10 mg OD and erythromycin (500 mg QID) resulted in a 33% increase in exposure to total atorvastatin activity.

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

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

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

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

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

**Grapefruit juice**: Contains one or more components that inhibit CYP3A4 and can increase plasma concentrations of drugs metabolised by CYP3A4. Intake of one 240 ml glass of grapefruit juice resulted in an increase in atorvastatin AUC of 37% and a decreased AUC of 20.4% for the active orthohydroxy metabolite. However, large quantities of grapefruit juice (over 1.2L daily for 5 days) increased AUC of atorvastatin 2.5 fold and AUC of active (atorvastatin and metabolites) HMG-CoA reductase inhibitors 1.3 fold. Concomitant intake of large quantities of grapefruit juice and atorvastatin is therefore not recommended.

**Inducers of cytochrome P450 3A4**: Concomitant administration of atorvastatin with inducers of cytochrome P450 3A4 (eg efavirenz, rifampin, St. John’s Wort) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, (cytochrome P450 3A4 induction and inhibition of hepatocyte uptake transporter OATP1B1), simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

**Verapamil and Amiodarone**: Interaction studies with atorvastatin and verapamil or amiodarone have not been conducted. Both verapamil and amiodarone are known to inhibit CYP3A4 activity and co-administration with atorvastatin may result in increased exposure to atorvastatin. Lipid levels should be monitored to ensure that the lowest dose necessary of atorvastatin is used.

**Other concomitant therapy**

**Gemfibrozil/fibrates**: The use of fibrates alone is occasionally associated with myopathy. The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibrates (see Section 4.4). Concomitant administration of gemfibrozil 600 mg BID resulted in a 24% increase in atorvastatin AUC.

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

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

**Colestipol**: Plasma concentrations of atorvastatin were lower (approximately 25%) when colestipol was administered with Lipitor. However, lipid effects were greater when Lipitor and colestipol were administered together than when either drug was given alone.

**Antacid**: Administration of Lipitor with an oral antacid suspension containing magnesium and aluminium hydroxides decreased atorvastatin plasma concentrations approximately 35%; however, LDL-C reduction was not altered.
Warfarin: Administration of Lipitor with warfarin caused a minimal decrease in prothrombin time (mean ± SE of 1.7 ± 0.4 seconds) during the first 4 days of dosing with 80 mg Lipitor. Dosing continued for 15 days and prothrombin time returned to normal by the end of Lipitor treatment. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor is added to their therapy.

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

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

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

Fusidic acid: Although interaction studies with atorvastatin and fusidic acid have not been conducted, severe muscle problems such as rhabdomyolysis have been reported in post-marketing experience with this combination. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

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

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 PREGNANCY AND LACTATION
Lipitor is contraindicated in pregnancy and while breast-feeding. Women of child-bearing potential should use appropriate contraceptive measures.

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

In animal studies atorvastatin had no effect on fertility and was not teratogenic, however, at maternally toxic doses foetal 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 atorvastatin equivalent to 6 and 21 times that expected in man, respectively.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
There is no pattern of reported adverse events suggesting that patients taking Lipitor will have any impairment of ability to drive and use hazardous machinery.

4.8 UNDESIRABLE EFFECTS
Adverse reactions have usually been mild and transient. In the atorvastatin placebo-controlled clinical trial database of 16,066 (8755 Lipitor vs. 7311 placebo) patients treated for a median period of 53 weeks, 5.2% of patients on atorvastatin discontinued due to adverse reactions compared to 4.0% of the patients on placebo.

The most frequent (1% or more) adverse effects that may be associated with Lipitor therapy, reported in patients participating in controlled clinical studies include:

Infections and infestations: nasopharyngitis

Metabolism and nutrition disorders: hyperglycemia
Respiratory, thoracic and mediastinal disorders: pharyngolaryngeal pain, epistaxis

Gastrointestinal disorders: abdominal pain, constipation, diarrhoea, dyspepsia, nausea, flatulence

Musculoskeletal and connective tissue disorders: arthralgia, pain in extremity, musculoskeletal pain, muscle spasms, myalgia, joint swelling

Investigations: liver function test abnormal, blood creatine phosphokinase increased

Psychiatric Disorders: insomnia

Nervous System Disorders: headache

General Disorders and Administration Site Conditions: asthenia

Elevated serum ALT levels have been reported in 1.3% of patients receiving Lipitor. Clinically important (>3 times upper normal limit) elevations in serum ALT levels occurred in 19 of the 2483 (0.8%) patients on Lipitor. It was dose related and was reversible in all 19 patients. In 10 cases, the increase was first observed within 12 weeks of starting the treatment. Only 1 case occurred after 36 weeks and only 1 patient had symptoms suggestive of hepatitis. Treatment was discontinued in only 9 of these 19 cases.

Elevated serum CPK levels (>3 times upper normal limit) occurred in 62 of the 2452 (2.5%) patients on Lipitor compared with 3.1% with other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in only 11 (0.4%) Lipitor-treated patients. Only 3 (0.1%) of these 11 patients had concurrent muscle pain, tenderness, or weakness.

Adverse events reported in atorvastatin clinical trials and in post marketing experience are categorised below according to system organ class and frequency. Frequencies are defined as: very common (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%) and very rare (<0.01%).

Gastrointestinal disorders
Common: constipation, flatulence, dyspepsia, nausea, diarrhoea
Uncommon: anorexia, vomiting, pancreatitis, abdominal discomfort
Rare: eructation

Blood and lymphatic system disorders
Uncommon: thrombocytopenia.

Immune system disorders
Common: allergic reactions (including anaphylaxis).

Endocrine disorders
Uncommon: alopecia, hyperglycaemia, hypoglycaemia.

Psychiatric
Common: insomnia.
Uncommon: amnesia, nightmare.

Nervous system disorders
Common: headache, dizziness, paraesthesia, hypoesthesia.
Uncommon: peripheral neuropathy.
Very rare: dysgeusia.

Eye disorders
Uncommon: vision blurred
Very rare: visual disturbance.
Hepato-biliary disorders
Rare: hepatitis, cholestasis.
Very rare: hepatic failure.

Skin/Appendages
Common: Skin rash, pruritus
Uncommon: urticaria, alopecia.
Very rare: angioneurotic oedema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis).

Ear and Labyrinth Disorders
Uncommon: tinnitus.
Very rare: hearing loss.

Musculoskeletal disorders
Common: myalgia, arthralgia.
Uncommon: myopathy, muscle cramps, neck pain.
Rare: myositis, rhabdomyolysis, muscle fatigue.
Very rare: tendon rupture.

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

General disorders
Common: asthenia, chest pain, back pain, fatigue.
Uncommon: malaise, weight gain.
Rare: peripheral oedema, pyrexia

Investigations
Rare: white blood cells urine positive
The following adverse events have been reported with some statins:

- Sleep disturbances, including insomnia and nightmares.
- Memory loss.
- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see Section 4.4).

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

Nervous system disorders
Common: Headache

Gastrointestinal disorders
Common: Abdominal pain

Investigations
Common: Alanine aminotransferase increased, blood creatine phosphokinase increased

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

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

5

PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles.

Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites (see Section 5.2 Pharmacokinetic Properties).

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides while producing variable increases in HDL-C in a dose-response study as shown in Table 1 below.

<table>
<thead>
<tr>
<th>Lipitor Dose (mg)</th>
<th>N</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>Apo-B</th>
<th>TG</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td></td>
<td>8</td>
<td>6</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>-30</td>
<td>-41</td>
<td>-34</td>
<td>-14</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>-35</td>
<td>-44</td>
<td>-36</td>
<td>-33</td>
<td>12</td>
</tr>
<tr>
<td>40</td>
<td>11</td>
<td>-38</td>
<td>-50</td>
<td>-41</td>
<td>-25</td>
<td>-3</td>
</tr>
<tr>
<td>80</td>
<td>11</td>
<td>-46</td>
<td>-61</td>
<td>-50</td>
<td>-27</td>
<td>3</td>
</tr>
</tbody>
</table>

Adjusted Mean % Change from Baseline

Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

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

Lipitor is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication. In a compassionate use study, 41 patients aged 6 to 51 years with homozygous familial hypercholesterolaemia or with severe hypercholesterolaemia, who had ≤15% reduction in LDL-C in response to previous maximum dose combination drug therapy, received daily doses of 40 to 80 mg of Lipitor. Twenty four patients with homozygous familial hypercholesterolaemia received 80 mg Lipitor. Nineteen of these 24 patients responded with a greater than 15% reduction of LDL-C (mean 26%, range 18% to 42%).

Atherosclerosis

11. In the Reversing Atherosclerosis with Aggressive Lipid-Lowering Study (REVERSAL), the effect of atorvastatin 80 mg and pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomized, double-blind, multicenter, controlled clinical trial, IVUS was performed at baseline and at 18 months in 502 patients. In the atorvastatin group (n=253), there was no progression of atherosclerosis evaluated by the percentage change in atheroma volume in a pre-defined target vessel with a stenosis
between 20% and 50%. 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).

12. 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).

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

The effect of intensive lipid lowering with atorvastatin on cardiovascular mortality and morbidity was not investigated in this 18-month study. Therefore, the clinical significance of these imaging results with regard to the primary and secondary prevention of cardiovascular events is unknown.

**Prevention of Cardiovascular Disease**

In the Anglo Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA), the effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤ 6.5mmol/l (251 mg/dl). Additionally, all patients had at least 3 of the predefined cardiovascular risk factors: male gender, age ≥ 55 years, smoking, diabetes, history of CHD in a first degree relative, TC:HDL ≥ 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria.

In this randomised, double-blind, placebo-controlled study, patients were treated with anti-hypertensive therapy and either atorvastatin 10mg daily (n=5168) or placebo (n=5137). After 3 years treatment with amlodipine or atenolol-based regimen, mean blood pressure fell from 164.2/94.9 to 138.9/80.1 mmHg (atorvastatin) and 164.2/94.3 to 138.9/80.0 mmHg (placebo).

After a median of 3.3 years of treatment, there was a statistically significant reduction in the rate of myocardial infarction (a component of the primary endpoint), 1.2% on atorvastatin versus 2.1% on placebo.

Fatal and non-fatal ischaemic strokes tended to be lower in the atorvastatin group with a relative risk reduction of 26% (89 vs. 119 events) and an absolute risk reduction of 0.6%. The difference did not reach pre-defined levels of statistical significance.

Women constituted 20% of the trial population and a subgroup analysis did not demonstrate any benefit on the primary endpoint of coronary events (fatal CHD plus non-fatal MI) (RR 1.11, 95% CI 0.58-2.13).

In the Collaborative Atorvastatin Diabetes Study (CARDS), the effect of atorvastatin on fatal and nonfatal cardiovascular disease was assessed in 2838 patients with type 2 diabetes 40-75 years of age, without prior history of cardiovascular disease and with LDL ≤ 4.14 mmol/l (160 mg/dl) and TG ≤ 6.78mmol/l (600mg/dl). Additionally, all patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

In this randomised, double-blind, multi-centre, placebo-controlled trial, patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk Reduction (%)</th>
<th>Absolute Risk Reduction (%)</th>
<th>No of events (atorvastatin vs.placebo)</th>
<th>p-value</th>
</tr>
</thead>
</table>

Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)  

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo %</th>
<th>Lipitor %</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (fatal and non-fatal AMI, silent MI)</td>
<td>42%</td>
<td>19%</td>
<td>0.007</td>
</tr>
<tr>
<td>Strokes (Fatal and non-fatal)</td>
<td>48%</td>
<td>13%</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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.

Although the relative risk reduction in the primary end-point was similar between men and women, the absolute benefit for the women was less since the primary event rate on placebo was approximately 1/3 of the male event rate.

Recurrence 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 haemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo.

• The risk of haemorrhagic stroke was increased in patients who entered the study with prior haemorrhagic stroke (7/45 for atorvastatin versus 2/48 for placebo; HR 4.06; 95% CI, 1.71-9.82).

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

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

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 hypercholesterolaemia 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

**Pharmacokinetics and Drug Metabolism**

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

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

**Metabolism:** Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. 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 and atorvastatin metabolites are substrates of P-glycoprotein (see section 4.5). Atorvastatin is eliminated primarily in bile following hepatic and/or extrahaepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

**Special Populations**
Geriatric: Plasma concentrations of atorvastatin 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 \( \geq 2 \) (N=24) paediatric patients (ages 6-17 years) with heterozygous familial hypercholesterolemia and baseline LDL-C \( \geq 4 \) 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 in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin.

Hepatic Insufficiency: Plasma concentrations of atorvastatin are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 PRECLINICAL SAFETY DATA
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8 to 16-fold higher based on AUC(0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC(0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Calcium carbonate
Microcrystalline cellulose
Crocarmellose sodium
Polysorbate 80
Magnesium stearate
Hydroxypropyl cellulose
Amylum pregelificatum
Mannitol (E421)
Aspartame (E951)
Sucralose (E955)
Grape flavour

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Blisters containing 30 chewable tablets. The blisters consist of a forming foil made of polyamide/aluminium foil/polyvinyl chloride and a backing made of aluminium foil/vinyl/acryl heat-seal coating.
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special instructions needed.

7 MARKETING AUTHORISATION HOLDER
Pfizer Ireland Pharmaceuticals
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER(S)
PL 16051/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/11/2010

10 DATE OF REVISION OF THE TEXT
03/11/2010
In this leaflet
1. What Lipitor is and what it is used for
2. Before you take Lipitor
3. How to take Lipitor
4. Possible side effects
5. How to store Lipitor
6. Further information

1. What Lipitor is and what it is used for

- Lipitor chewable tablets are white to off-white with pink to purple specks with a round shape. They are marked with 5, 10, 20 or 40 on one side and Pfizer on the other side.
- Lipitor is used in adults and children aged 10 years and above. The active ingredient is atorvastatin.
- Lipitor belongs to a group of medicines known as lipid (fat) regulating medicines commonly known as statins.
- Lipitor is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and lifestyle changes on their own have failed. Cholesterol is a naturally occurring substance in the body necessary for normal growth. However, if there is too much cholesterol in your blood it can be deposited in the walls of blood vessels leading to the narrowing of these vessels, which may eventually become blocked. This is one of the most common causes of heart disease. It is accepted that raised cholesterol levels increase the risk of heart disease.
- If you are diabetic and have at least one other risk factor for cardiovascular disease, Lipitor reduces the risk of you having a major cardiovascular event such as a heart attack or a stroke.
- Remember to continue with your diet and lifestyle changes while you are taking Lipitor.
2. Before you take Lipitor

Do not take Lipitor

- If you are a woman able to have children and not using reliable contraception
- If you are pregnant, trying to become pregnant or breast-feeding
- If you are trying to become pregnant your doctor will advise you to stop taking Lipitor about one month before you plan to conceive.
- If you have ever had a reaction to Lipitor or to any similar medicines used to lower blood lipids or to any of the inactive ingredients of the medicine - see Section 5 for details
- If you have or have ever had a disease which affects the liver
- If you have had any unexplained abnormal blood tests for liver function
- If you drink excessive amounts of alcohol.

Take special care with Lipitor

The following are reasons why Lipitor may not be suitable for you:

- If you have kidney problems or a history of kidney problems.
- If you have an under-active thyroid gland (hypothyroidism)
- If you have muscle disorders (affecting either yourself or other members of your family)
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other ‘-statin’ or ‘-fibrate’ medicines)
- If you have a history of heavy alcohol consumption
- If you are older than 70 years
- If you have serious problems with your breathing.

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

Tell your doctor if you have ever had any type of stroke; your doctor will need to consider this in deciding the best treatment and dose for you.

Important information about some of the ingredients of Lipitor

Contains a source of phenylalanine. May be harmful for people with phenylketonuria.

Taking other medicines

There are some medicines that may change the effect of Lipitor, or their effect may be changed by Lipitor. This type of interaction could make one or both of the medicines less effective. Alternatively it could increase the risk or severity of side-effects, including the important but rare muscle wasting condition known as rhabdomyolysis (see below). Your doctor will consider this in deciding upon your dose of Lipitor.

There are some medicines that may interact with Lipitor:

- Medicines used to alter the way your immune system works, e.g. ciclosporin or antihistamines such as terfenadine, astemizole
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole, rifampicin, fusidic acid (also known as sodium fusidate)
- Other medicines to regulate lipid levels, e.g. gemfibrozil, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. verapamil, diltiazem
- Medicines to regulate your heart rhythm e.g. digoxin, amiodarone
- Protease inhibitors used in the treatment of HIV e.g. nelfinavir
• Other medicines known to interact with Lipitor include warfarin (which reduces blood clotting), oral contraceptives and antacids (indigestion products containing aluminium or magnesium) and St John’s Wort.

You should always tell your doctor if you are taking or have recently taken any other medicine, even those not prescribed, because they might interact.

**Taking Lipitor with food and drink**
When taking Lipitor, do not drink more than one or two small glasses of grapefruit juice per day.

**Pregnancy**
Do not take Lipitor if you are pregnant or trying to become pregnant.

**Breast-feeding**
Do not take Lipitor if you are breast-feeding.

**Driving and using machinery**
It is not expected that Lipitor will affect your ability to drive or operate machinery.

### 3. How to take Lipitor

The usual starting dose of Lipitor 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.

The maximum dose of Lipitor is 80 mg once daily for adults and 20 mg once daily for children.

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

**If you take more Lipitor than you should:**
If you accidentally take too many Lipitor Tablets (more than your usual daily dose), tell your doctor at once.

**If you miss a dose of Lipitor:**
If you forget to take a dose, take it as soon as you remember unless it is time for your next dose.

Do not take 2 doses at the same time.

### 4. Possible side effects

The following side effects are important and will require immediate action if you experience them:

• Angioneurotic oedema (swelling of the face, tongue and windpipe which can cause great difficulty in breathing). This is a very rare reaction, which can be serious if it occurs. You should tell your doctor immediately if it happens.

• Occasionally, patients have developed muscle wasting or inflammation, and very rarely this has progressed to become a serious, potentially life-threatening condition (called ‘rhabdomyolysis’). If you have muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell or have a high temperature, stop taking Lipitor and tell your doctor immediately.

**Very rare conditions** affect fewer than 1 in 10,000 patients taking Lipitor (this means that for every 10,000 patients taking Lipitor, 9,999 are not expected to have these side effects).

• If you experience problems with unexpected or unusual bleeding or bruising, this may be suggestive of a liver complaint. You should consult your doctor as soon as possible.

**Other possible side effects with Lipitor:**
As with all medicines, Lipitor can sometimes cause side effects in some individuals.

**Common conditions** affect at least 100 in 10,000 patients taking Lipitor (this means that for every 10,000 patients, up to 9,900 are not expected to have these side effects).

You will find more about **LIPITOR on the back of this leaflet**
These include:
- Stuffy or runny nose due to inflammation, high levels of sugar in the blood (if you have diabetes you should continue careful monitoring of your blood sugar levels), sore throat, nose bleed, feeling sick (nausea), abdominal pain, constipation, wind, indigestion, headache, muscle, bone or joint pain, joint swelling, muscle spasms, pain in the hands and feet, changes to the results of blood tests, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions (including severe allergic reaction), skin rash, itching, numbness or pins and needles, tiredness and back pain.

Other less common side effects have been seen in some patients taking Lipitor or other medicines of this kind. Not all of these effects have necessarily been linked to the use of these medicines.

Uncommon conditions affect fewer than 100 in 10,000 patients taking Lipitor (this means that for every 10,000 patients taking Lipitor, at least 9,999 are not expected to have these side effects).

These include:
- Nightmare, anorexia (loss of appetite), being sick, numbness or tingling in the fingers and toes, pancreatitis (inflammation of the pancreas leading to stomach pain), abdominal pain or discomfort, reductions in sensation of skin to light touch or pain, itching; rash, hives, muscle cramps, muscle weakness, neck pain, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, itchy rash; feeling unwell, impotence, hair loss, blurred vision. Decreases in blood sugar levels have also been seen (If you have diabetes you should continue careful monitoring of your blood sugar levels).

Rare conditions affect fewer than 10 in 10,000 patients taking Lipitor (this means that for every 10,000 patients taking Lipitor, at least 9,999 are not expected to have these side effects).

These include:
- Belching, peripheral oedema (e.g. ankle swelling), muscle tenderness or cramps, blistering rash, hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes), tired or weak muscles, fever, white blood cells in the urine, rhabdomyolysis (serious muscle pain and weakness, often associated with fever).

Very rare conditions affect fewer than 1 in 10,000 patients taking Lipitor (this means that for every 10,000 patients taking Lipitor, at least 9,999 are not expected to have these side effects).

These include:
- Angioneurotic oedema (swelling of the face, tongue and windpipe which can cause great difficulty in breathing), Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals), erythema multiforme (patchy red rash), visual disturbance, hearing loss, tendon injury, liver failure, change in sense of taste, breast enlargement in men.

Other side effects reported with statins (medicines of the same type as Lipitor) are:
Sleep disturbances including insomnia and nightmares, memory loss, sexual difficulties, depression and problems with breathing including persistent cough, shortness of breath and fever.

If you get any of these, or any other unusual effects, tell your doctor or pharmacist at once.

5. How to store Lipitor

Keep out of reach and sight of children.
Store in the original package at room temperature.
Do not use after the last day of the month shown in the expiry date on the carton and blister.
6. Further Information

Lipitor package and contents
The active substance of Lipitor is atorvastatin. Each chewable tablet contains 5 mg, 10 mg, 20 mg, or 40 mg of atorvastatin as atorvastatin calcium trihydrate.

Lipitor tablets also contain the inactive ingredients: calcium carbonate, microcrystalline cellulose, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose, amyloid pregelificatum, mannitol, aspartame, sucralose, grape flavour and magnesium stearate.

Each strength of Lipitor is supplied in blister packs of 30 tablets.

This medicine is available as 5 mg, 10 mg, 20 mg and 40 mg chewable tablets and 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets.

Please note that not all the above presentations may be marketed.

Marketing Authorisation Holder
Pfizer Ireland Pharmaceuticals, Pottery Road, Dun Laoghaire, Co. Dublin, Ireland.

Manufacturer
Pfizer Manufacturing Deutschland GmbH, Mooswaldallee 1, D-79090 Freiburg, Germany.
Lipitor is also known as Cardyl, Sortis, Tahir, Torvast & Zarator

Company contact address:
Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey, KT20 7NS.
Telephone 01304 616161.

Leaflet was last updated: September 2010. Ref: LR 1_1

Some Helpful Advice
In addition to taking this medicine as your doctor instructed, there are many other things you can do to help yourself. Your doctor may have explained some of them. The most important steps are the following, which have been drawn up by Heart UK

• See your doctor or nurse regularly for check-ups.
• Stop smoking. Free phone line 0800 002200 or website www.quit.org
• Free Heart UK Fact Sheet available with SAE.
• Reduce saturated fats. Replace some saturates with monounsaturates and polyunsaturates (Free Guide to Healthy Eating available from Heart UK with SAE).
• Take regular physical activity such as walking, swimming or dancing - not violent activities such as squash or weightlifting. Sex is fine as well. Ask your doctor how much you can safely do. If you get chest pain or become breathless, stop and rest. (Free Heart UK leaflet with SAE).
• Go easy on alcohol.
• Keep to a healthy body weight.
• Relax and laugh!

For more information or advice, you may like to contact Heart UK.

• Heart UK provides information and advice for patients mainly through a magazine, The Digest, published four times a year, Fact Sheets and a Helpline.
• Heart UK specialises in blood, cholesterol and other lipid disorders, especially inherited high cholesterol, familial hypercholesterolaemia, familial combined hyperlipidaemia and polygenic hyperlipidaemia.

You can join Heart UK. For membership details or publications contact:
Heart UK,
7 North Road,
Maidenhead,
Berkshire,
SL6 1PL.
Helpline number: 0845 450 5988.
UKPAR Lipitor 5mg, 10mg, 20mg and 40mg Chewable Tablets

Pfizer
Lipitor™ 5 mg Chewable Tablets
Atorvastatin

1 chewable tablet contains 5 mg atorvastatin (as calcium salt trihydrate).
Contains aspartame.
Read the package leaflet before use.
Oral use. Use as directed by a doctor.
Keep out of the reach and sight of children.
1 chewable tablet contains 10 mg atorvastatin (as calcium salt trihydrate).
Contains aspartame.
Read the package leaflet before use.
Oral use. Use as directed by a doctor.
Keep out of the reach and sight of children.
Lipitor Chewable Tablets
Atorvastatin

1 chewable tablet contains 20 mg atorvastatin (as calcium salt trihydrate).
Contains aspartame.
Read the package leaflet before use.
Oral use. Use as directed by a doctor.
Keep out of the reach and sight of children.
UKPAR Lipitor 5mg, 10mg, 20mg and 40mg Chewable Tablets

1 chewable tablet contains 40 mg atorvastatin (as calcium salt trihydrate).
Contains aspartame.
Read the package leaflet before use.
Oral use. Use as directed by a doctor.
Keep out of the reach and sight of children.