ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Austria	Pfizer Corporation Austria Ges.m.b.H.	Sortis	10mg	Film-coated tablet	Oral use
Austria	Pfizer Corporation Austria Ges.m.b.H.	Sortis	20mg	Film-coated tablet	Oral use
Austria	Pfizer Corporation Austria Ges.m.b.H.	Sortis	40mg	Film-coated tablet	Oral use
Austria	Pfizer Corporation Austria Ges.m.b.H.	Sortis	80mg	Film-coated tablet	Oral use
Belgium	Pfizer S.A.	Lipitor	10mg	Film-coated tablet	Oral use
Belgium	Pfizer S.A.	Lipitor	20mg	Film-coated tablet	Oral use
Belgium	Pfizer S.A.	Lipitor	40mg	Film-coated tablet	Oral use
Belgium	Pfizer S.A.	Lipitor	80mg	Film-coated tablet	Oral use
Denmark	Pfizer ApS	Zarator	10mg	Film-coated tablet	Oral use
Denmark	Pfizer ApS	Zarator	20mg	Film-coated tablet	Oral use
Denmark	Pfizer ApS	Zarator	40mg	Film-coated tablet	Oral use
Denmark	Pfizer ApS	Zarator	80mg	Film-coated tablet	Oral use
Finland	Pfizer Oy	Lipitor	10mg	Film-coated tablet	Oral use
Finland	Pfizer Oy	Lipitor	20mg	Film-coated tablet	Oral use
Finland	Pfizer Oy	Lipitor	40mg	Film-coated tablet	Oral use
Finland	Pfizer Oy	Lipitor	80mg	Film-coated tablet	Oral use
Germany	PARKE-DAVIS GmbH	Sortis	10mg	Film-coated tablet	Oral use
Germany	PARKE-DAVIS GmbH	Sortis	20mg	Film-coated tablet	Oral use
Germany	PARKE-DAVIS GmbH	Sortis	40mg	Film-coated tablet	Oral use
Germany	PARKE-DAVIS GmbH	Sortis	80mg	Film-coated tablet	Oral use
Greece	Pfizer Hellas AE	Lipitor	10mg	Film-coated tablet	Oral use
Greece	Pfizer Hellas AE	Lipitor	20mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Greece	Pfizer Hellas AE	Lipitor	40mg	Film-coated tablet	Oral use
Greece	Pfizer Hellas AE	Lipitor	80mg	Film-coated tablet	Oral use
Italy	PARKE-DAVIS SpA	Xarator	10mg	Film-coated tablet	Oral use
Italy	PARKE-DAVIS SpA	Xarator	20mg	Film-coated tablet	Oral use
Italy	PARKE-DAVIS SpA	Xarator	40mg	Film-coated tablet	Oral use
Italy	PARKE-DAVIS SpA	Xarator	80mg	Film-coated tablet	Oral use
Luxembourg	Pfizer S.A.	Lipitor	10mg	Film-coated tablet	Oral use
Luxembourg	Pfizer S.A.	Lipitor	20mg	Film-coated tablet	Oral use
Luxembourg	Pfizer S.A.	Lipitor	40mg	Film-coated tablet	Oral use
Luxembourg	Pfizer S.A.	Lipitor	80mg	Film-coated tablet	Oral use
Netherlands	Pfizer bv	Lipitor	10mg	Film-coated tablet	Oral use
Netherlands	Pfizer bv	Lipitor	20mg	Film-coated tablet	Oral use
Netherlands	Pfizer bv	Lipitor	40mg	Film-coated tablet	Oral use
Netherlands	Pfizer bv	Lipitor	80mg	Film-coated tablet	Oral use
Portugal	Laboratórios Pfizer, Lda	Zarator	10mg	Film-coated tablet	Oral use
Portugal	Laboratórios Pfizer, Lda	Zarator	20mg	Film-coated tablet	Oral use
Portugal	Laboratórios Pfizer, Lda	Zarator	40mg	Film-coated tablet	Oral use
Portugal	Laboratórios Pfizer, Lda	Zarator	80mg	Film-coated tablet	Oral use
Spain	PARKE-DAVIS, S.L.	Zarator	10mg	Film-coated tablet	Oral use
Spain	PARKE-DAVIS, S.L.	Zarator	20mg	Film-coated tablet	Oral use
Spain	PARKE-DAVIS, S.L.	Zarator	40mg	Film-coated tablet	Oral use
Spain	PARKE-DAVIS, S.L.	Zarator	80mg	Film-coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented name	Strength	Pharmaceutical form	Route of administration
Sweden	Pfizer AB	Lipitor	10mg	Film-coated tablet	Oral use
Sweden	Pfizer AB	Lipitor	20mg	Film-coated tablet	Oral use
Sweden	Pfizer AB	Lipitor	40mg	Film-coated tablet	Oral use
Sweden	Pfizer AB	Lipitor	80mg	Film-coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ATORVASTATIN
(Sortis and associated names - see Annex I)

Sortis and associated names contain atorvastatin, a well-known HMG-CoA reductase inhibitor (statin), registered in the EU since 1996 through Mutual Recognition Procedure and national procedures. The currently approved indications for atorvastatin are:

- as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and tryglicerides in patients with primary hypercholesterolemia including familial hypercholesterolemia (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.
- to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Background information on the type II variation through the MRP

In the initial type II variation dossier submitted by MRP, the Applicant claimed the following indication:
"Prevention of cardiovascular events in patients with multiple risk factors (e.g. type 2 diabetics with one risk factor and hypertensive patients with 3 risk factors) with normal or elevated cholesterol levels but without clinically evident coronary heart disease (CHD)".

This wording was based on the results of 2 randomised controlled trials performed with atorvastatin 10 mg for the primary prevention of cardiovascular disease (CVD). The ASCOT-LLA study was carried out in 10,000 patients (40-79 years of age) with normal to mildly elevated cholesterol levels, no previous MI or treatment for angina but with hypertension and at least 3 other CV risk factors, to assess the effect of atorvastatin on fatal and non-fatal CHD. Atorvastatin significantly reduced the frequency of coronary and CV events, strokes and revascularisation procedures in the entire study cohort. However, in the subgroup analyses by gender (81% males, 19% females), a beneficial effect of atorvastatin was seen in males but could not be established in females, and overall mortality and CV mortality were numerically higher (not significant) in the female patients. The CARDS study was conducted in 2,838 patients (40-75 years of age) with normal to mildly elevated cholesterol levels, with type 2 diabetes and 1 additional CV risk factor, and without clinically evident CHD. Atorvastatin significantly reduced the frequency of major CV events, the frequency of fatal, non-fatal AMI and silent MI and the frequency of strokes.

In the Final Assessment report (1 November 2005) the Reference Member State proposed, and the MAH agreed to, the following indication :
"Prevention of cardiovascular events in patients with type 2 diabetes and one additional risk factor with normal to mildly elevated cholesterol level without clinically evident coronary heart disease".

thus restricting the indication to the population included in the CARDs trial and relegating the results of the ASCOT-LLA trial to a description in section 5.1. of the SPC, based on the lack of demonstrated efficacy in the female subgroup.

At the end of the MRP procedure there was a discrepancy between Member States regarding the wording of the proposed indication that adequately reflects the data of the ASCOT-LLA and CARDS studies, effectively excluding treatment in non-diabetics, and an official referral for arbitration was notified by Spain to the CHMP on 1 December 2005. At the December plenary meeting, the CHMP adopted a LoQ centred on the following points:

1. How to adequately reflect in the SPC the lack of a significant effect in favour of atorvastatin for the composite primary endpoint and several secondary endpoints in the female subgroup.

2. Whether to exclude the target population of the ASCOT-LLA study from the proposed

indication, thus precluding the treatment of non-diabetic patients at high cardiovascular risk.

3. Whether the cardioprotective effect of atorvastatin is higher when used in combination with particular antihipertensive therapy(ies) and whether this should be reflected in the SPC.

4. To what extent the claimed therapeutic indication could be applied to atorvastatin doses other than the one tested in the CARDS and ASCOT-LLA trials.

5. An overview of the approved indications for atorvastatin based on the ASCOT-LLA and CARDS studies across the EU.

Evaluation of Clinical Efficacy

The main issue discussed by the CHMP has been the results of the ASCOT-LLA trial, most importantly the lack of established benefit and adverse mortality trends in the female subgroup and, secondly, the impact of the observed interaction between the antihypertensive amlodipine and atorvastatin on the main trial outcomes for certain subgroups. Atorvastatin significantly reduced the frequency of coronary and CV events, strokes and revascularisation procedures in the entire study cohort, but a beneficial effect in the female subgroup could not be established, and overall mortality and CV mortality were numerically higher (not significant) in female patients. In order to put the results from ASCOT-LLA into a wider perspective and to further support the safety and benefit of atorvastatin in the primary prevention of CV events, regardless of gender, the Applicant has provided i) a brief review of data with respect to gender from other statin clinical trials, ii) the current position of scientific societies on the recommended management of CVD in women, iii) key results by gender for ASCOT-LLA and CARDS, highlighting similarities between the studies, and iv) reference to current regulatory guidance and scientific limitations in interpreting results from subgroup analyses.

The Applicant has presented arguments for the view that the results for women in ASCOT-LLA based on subgroup analyses are most likely chance findings and are not considered scientifically robust enough to form the basis for regulatory actions. Moreover, the Applicant has provided an adequate and objective justification against a restriction to exclude women from the proposed indication given the current knowledge regarding the beneficial effects of statin treatment overall and also in women, including trial results, guidelines and international recommendations.

The main concern relates to the “risk of CVD”. It is obvious that the age-adjusted absolute benefit of primary CVD prevention is much lower in women than in men, as women have a lower CVD risk at the same age. In order to get the same absolute efficacy of atorvastatin in both sexes, it is therefore necessary to treat women who have the same absolute risk as men, i.e. women with more additional risk factors, such as higher age, menopause, etc. The physician should bear in mind that the decision to treat women should be based not only on clinical treatment guidelines but also on the determination of the absolute CV risk taking into account gender, age, smoking, blood pressure, cholesterol, etc (e.g. using Score and Framingham). Therefore, the CHMP agrees that excluding females from the indication would deprive an important sub-group of the population of atorvastatin treatment if their CV risk warrants this treatment, and believes the above findings in the female subgroup of ASCOT-LLA should be reflected in section 5.1 of the SPC.

Regarding the interaction observed between atorvastatin and amlodipine, the body of data assessed indicates that this interaction is of questionable clinical relevance, if it exists at all, and does not warrant regulatory action dictating the prescription of the product. Nonetheless, the CHMP thought it relevant to reflect this finding and include following factual statement in the pragraph summarising the results of ASCOT-LLA under section 5.1 of the SPC.

A point of minor discussion was the applicability of the trial results to other strengths of atorvastatin. The CHMP agrees that there is no reason to believe that higher doses would have a lower effect than the 10mg dose in the approved indication, independently of individual target cholesterol levels, and the potentially different safety profile of higher dosages. The appropriate place for dose

recommendations is section 4.2 of the SPC, not section 4.1, and adequate dosing recommendations have been added.

Finally, there has been much discussion regarding the wording of the indication that best reflects the results of the of the assessed trials. Despite agreeing to the Applicant's request not to exclude females and non-diabetics from the indication, the CHMP regards the claimed indication, which mirrors the ASCOT-LLA and CARDS patient populations, to be too broad. Indeed, many of the patients were at low risk, particularly the females in ASCOT-LLA. The trial results show that for some low risk subgroups included in the studies, corresponding to large populations, treatment is probably not justified with current knowledge, and approving such an indication would result in the treatment of many patients that have no benefit from lipid lowering therapy. Therefore, the CHMP favours restricting the indication to patients who have a high risk for a first cardiovascular event, thus forcing the prescriber to perform an individual risk assessment rather than following an algorithm for decision on treatment.

In the light of the above the CHMP concludes that the indication for atorvastatin *"Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event, as an adjunct to correction of other risk factors."* adequately reflects the available data.

Overall conclusion on benefit/risk

At its meeting of 20-23 March 2006, the CHMP considered the data on efficacy presented by the MAHs and concluded that it had been shown that atorvastatin, as an adjunct to correction of other risk factors, was effective in the prevention of CV events in patients estimated to have a high risk for a first CV event.

The CHMP recommended the granting of the type II variation to extend the indication.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the CHMP considered the referral made under article 6.12 of Commission Regulation (EC) No 1084/2003, for atorvastatin (Sortis and associated names - see Annex I),
- The MAH has implemented the text proposed by the CHMP in the SPC:
  - It is proposed to add the following indication in section 4.1:
    Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1), as an adjunct to correction of other risk factors.
  - The posology in Section 4.2 has been revised as follows:
    In the primary prevention trials the dose was 10 mg/day. Higher dosages may be necessary in order to attain (LDL-)cholesterol levels according to current guidelines.
  - Section 5.1 has been updated to include the results of the ASCOT-LLA and CARDS trials as follows:
    Prevention of Cardiovascular Disease
    The effect of atorvastatin on fatal and non-fatal coronary heart disease was assessed in a randomised, double-blind, placebo-controlled study, the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm (ASCOT-LLA). Patients were hypertensive, 40-79 years of age, with no previous myocardial infarction or treatment for angina, and with TC levels ≤6.5 mmol/l (251 mg/dl). All patients had at least 3 of the pre-defined cardiovascular risk factors: male gender, age ≥55 years, smoking, diabetes, history of CHD in a first-degree relative, TC:HDL-C >6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific ECG abnormality, proteinuria/albuminuria. Not all included patients were estimated to have a high risk for a first cardiovascular event.

Patients were treated with anti-hypertensive therapy (either amlodipine or atenolol-based regimen) and either atorvastatin 10 mg daily (n=5168) or placebo (n=5137).

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

Event	Relative Risk Reduction (%)	No. of Events (Sortis vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36 %	100 vs. 154	1.1 %	0.0005
Total cardiovascular events and revascularization procedures	20 %	389 vs. 483	1.9 %	0.0008
Total coronary events	29 %	178 vs 247	1.4 %	0.0006

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

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

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomised, double-blind, multicentre, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of cardiovascular disease, and with LDL-C ≤4.14 mmol/l (160 mg/dl) and TG≤6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

Event	Relative Risk Reduction (%)	No. of Events (Sortis vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularisation, stroke)	37 %	83 vs. 127	3.2 %	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs 64	1.9 %	0.0070
Strokes (Fatal and non-fatal)	48 %	21 vs. 39	1.3 %	0.0163

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

There was no evidence of a difference in the treatment effect by patient's gender, age, or baseline LDL-C level. A favourable trend was observed regarding the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).
A relative risk reduction in death of 27% (82 deaths in the placebo group compared to 61 deaths in the atorvastatin group) was observed with a borderline statistical significance (p=0.0592).

- no untoward safety findings related to the extension of the indication have been identified.

- the CHMP, as a consequence, considered the benefit/risk balance for the above-mentioned extension of indication to be favourable,

The CHMP has recommended the granting of the variation of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and Package Leaflet are set out in Annex III for atorvastatin (Sortis and related names - see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

<[See Annex I - To be completed nationally]> *[For referral procedures]*
{PRODUCT NAME} 10 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

Each {PRODUCT NAME} 10 mg film-coated tablet contains 32.80 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White elliptical, film-coated tablets debossed "10" on one side and "PD 155" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

{PRODUCT NAME} is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

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

Prevention of cardiovascular disease

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

4.2 Posology and method of administration

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

Dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.

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

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

For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatment goal is LDL-C < 3 mmol/l (or < 115 mg/dl) and total cholesterol < 5 mmol/l (or < 190 mg/dl).

Adapted from "Prevention of coronary heart disease in clinical practice:
Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention" in Atherosclerosis 140 (1998) 199-270.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with {PRODUCT NAME} 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

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

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

Prevention of cardiovascular disease

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

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations nor lipid effects of {PRODUCT NAME}; thus, no adjustment of dose is required.

Geriatric use

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

Pediatric use

Pediatric use should only be carried out by specialists.
Experience in pediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

{PRODUCT NAME} is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breast-feeding
- 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 transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of {PRODUCT NAME} is recommended (see section 4.8).

{PRODUCT NAME} should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle effects

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

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

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

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

Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Interaction may occur when {PRODUCT NAME} is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see section 4.4).

Inhibitors of P-glycoprotein

Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. ciclosporin) can increase the bioavailability of atorvastatin.

Erythromycin, clarithromycin

Coadministration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the Cmax and AUC of atorvastatin by 56% and 80% respectively.

Itraconazole

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 3-fold increase in atorvastatin AUC.

Protease inhibitors

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

Grapefruit juice

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

Inducers of cytochrome P450 3A4

The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on {PRODUCT NAME} is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other medicinal products with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.

Other concomitant therapy

Gemfibrozil / fibric acid derivatives
The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibric acid derivatives. According to results of in vitro studies the metabolic pathway of atorvastatin via glucuronidation is inhibited by Gemfibrozil. This may possibly lead to increased plasma levels of atorvastatin (see section 4.4).

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking digoxin should be monitored appropriately.

Oral contraceptives
Coadministration of {PRODUCT NAME} with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with {PRODUCT NAME}. However, lipid effects were greater when {PRODUCT NAME} and colestipol were coadministered than when either medicinal product was given alone.

Antacid
Coadministration of {PRODUCT NAME} with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approx. 35%; however, LDL-C reduction was not altered.

Warfarin
Coadministration of {PRODUCT NAME} and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of {PRODUCT NAME} treatment. Nevertheless, patients receiving warfarin should be closely monitored when {PRODUCT NAME} is added to their therapy.

Phenazone
Coadministration of multiple doses of {PRODUCT NAME} and phenazone showed little or no detectable effect in the clearance of phenazone.

Cimetidine
An interaction study with cimetidine and {PRODUCT NAME} was conducted, and no interaction was seen.

Amlodipine
Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Other
In clinical studies in which {PRODUCT NAME} was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

{PRODUCT NAME} is contraindicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

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

4.7 Effects on ability to drive and use machines

{PRODUCT NAME} has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Less than 2% of patients were discontinued from clinical trials due to side effects attributed to {PRODUCT NAME}.

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

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

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: anorexia, vomiting.

Blood and lymphatic system disorders

Uncommon: thrombocytopenia.

Immune system disorders

Common: allergic reactions.
Very rare: anaphylaxis.

Endocrine disorders

Uncommon: alopecia, hyperglycaemia, hypoglycaemia, pancreatitis.

Psychiatric

Common: insomnia.
Uncommon: amnesia.

Nervous system disorders

Common: headache, dizziness, paraesthaesia, hypoesthesia.
Uncommon: peripheral neuropathy.

Hepato-biliary disorders

Rare: hepatitis, cholestatic jaundice.

Skin/Appendages

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

Ear and Labyrinth Disorders

Uncommon: tinnitus

Musculoskeletal disorders

Common: myalgia, arthralgia.
Uncommon: myopathy.
Rare: myositis, rhabdomyolysis.

Reproductive system disorders

Uncommon: impotence.

General disorders

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

Investigations

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, ATC code: C10AA05

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

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

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

homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet completed.

Atherosclerosis

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

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

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

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

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

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

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

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

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of

cardiovascular disease, and with LDL-C ≤4.14 mmol/l (160 mg/dl) and TG ≤6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

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

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

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

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

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism

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

Excretion

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

Special populations

- Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: Pharmacokinetic data in the paediatric population are not available.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
- Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$. Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Polysorbate 80
Hyprolose
Magnesium stearate

Film coating

Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Talc
Simethicone
Stearate emulsifiers
Sorbic acid
Candelilla wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets.
Hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

The blisters consist of a forming film made of polyamide/aluminum foil/polyvinyl chloride and a backing made of either paper/polyester/aluminum foil/vinyl heat-seal coating or aluminum foil/vinyl heat-seal coating.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<[See Annex I - To be completed nationally]> *[For referral procedures]*
{PRODUCT NAME} 20mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

Each {PRODUCT NAME} 20 mg film-coated tablet contains 65.61 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White elliptical, film-coated tablets debossed "20" on one side and "PD 156" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

{PRODUCT NAME} is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

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

Prevention of cardiovascular disease

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

4.2 Posology and method of administration

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

Dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.

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

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

For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatment goal is LDL-C < 3 mmol/l (or < 115 mg/dl) and total cholesterol < 5 mmol/l (or < 190 mg/dl).

Adapted from "Prevention of coronary heart disease in clinical practice:
Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention" in Atherosclerosis 140 (1998) 199-270.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with {PRODUCT NAME} 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

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

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

Prevention of cardiovascular disease

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

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations nor lipid effects of {PRODUCT NAME}; thus, no adjustment of dose is required.

Geriatric use

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

Pediatric use

Pediatric use should only be carried out by specialists.
Experience in pediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

{PRODUCT NAME} is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breast-feeding
- 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 transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of {PRODUCT NAME} is recommended (see section 4.8).

{PRODUCT NAME} should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle effects

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

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

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

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

Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Interaction may occur when {PRODUCT NAME} is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see section 4.4).

Inhibitors of P-glycoprotein

Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. ciclosporin) can increase the bioavailability of atorvastatin.

Erythromycin, clarithromycin

Coadministration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the Cmax and AUC of atorvastatin by 56% and 80% respectively.

Itraconazole

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 3-fold increase in atorvastatin AUC.

Protease inhibitors

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

Grapefruit juice

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

Inducers of cytochrome P450 3A4

The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on {PRODUCT NAME} is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other medicinal products with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.

Other concomitant therapy

Gemfibrozil / fibric acid derivatives
The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibric acid derivatives. According to results of in vitro studies the metabolic pathway of atorvastatin via glucuronidation is inhibited by Gemfibrozil. This may possibly lead to increased plasma levels of atorvastatin (see section 4.4).

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking digoxin should be monitored appropriately.

Oral contraceptives
Coadministration of {PRODUCT NAME} with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with {PRODUCT NAME}. However, lipid effects were greater when {PRODUCT NAME} and colestipol were coadministered than when either medicinal product was given alone.

Antacid
Coadministration of {PRODUCT NAME} with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approx. 35%; however, LDL-C reduction was not altered.

Warfarin
Coadministration of {PRODUCT NAME} and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of {PRODUCT NAME} treatment. Nevertheless, patients receiving warfarin should be closely monitored when {PRODUCT NAME} is added to their therapy.

Phenazone
Coadministration of multiple doses of {PRODUCT NAME} and phenazone showed little or no detectable effect in the clearance of phenazone.

Cimetidine
An interaction study with cimetidine and {PRODUCT NAME} was conducted, and no interaction was seen.

Amlodipine
Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Other
In clinical studies in which {PRODUCT NAME} was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.8 Pregnancy and lactation

{PRODUCT NAME} is contraindicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

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

4.7 Effects on ability to drive and use machines

{PRODUCT NAME} has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Less than 2% of patients were discontinued from clinical trials due to side effects attributed to {PRODUCT NAME}.

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

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

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: anorexia, vomiting.

Blood and lymphatic system disorders

Uncommon: thrombocytopenia.

Immune system disorders

Common: allergic reactions.
Very rare: anaphylaxis.

Endocrine disorders

Uncommon: alopecia, hyperglycaemia, hypoglycaemia, pancreatitis.

Psychiatric

Common: insomnia.
Uncommon: amnesia.

Nervous system disorders

Common: headache, dizziness, paraesthaesia, hypoesthesia.
Uncommon: peripheral neuropathy.

Hepato-biliary disorders

Rare: hepatitis, cholestatic jaundice.

Skin/Appendages

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

Ear and Labyrinth Disorders

Uncommon: tinnitus

Musculoskeletal disorders

Common: myalgia, arthralgia.
Uncommon: myopathy.
Rare: myositis, rhabdomyolysis.

Reproductive system disorders

Uncommon: impotence.

General disorders

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

Investigations

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, ATC code: C10AA05

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

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

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

homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet completed.

Atherosclerosis

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

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

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

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

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

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

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

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

The effect of atorvastatin on fatal and non-fatal cardiovascular disease was also assessed in a randomized, double-blind, multicenter, placebo-controlled trial, the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes, 40-75 years of age, without prior history of

cardiovascular disease, and with LDL-C ≤4.14 mmol/l (160 mg/dl) and TG ≤6.78 mmol/l (600 mg/dl). All patients had at least 1 of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years.

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37 %	83 vs. 127	3.2 %	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs 64	1.9 %	0.0070
Strokes (Fatal and non-fatal)	48 %	21 vs. 39	1.3 %	0.0163

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

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

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism

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

Excretion

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

Special populations

- Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: Pharmacokinetic data in the paediatric population are not available.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10 % lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
- Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6-to 11-fold higher based on $AUC_{(0-24)}$. Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Polysorbate 80
Hyprolose
Magnesium stearate

Film coating

Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Talc
Simethicone
Stearate emulsifiers
Sorbic acid
Candelilla wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets.
Hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

The blisters consist of a forming film made of polyamide/aluminum foil/polyvinyl chloride and a backing made of either paper/polyester/aluminum foil/vinyl heat-seal coating or aluminum foil/vinyl heat-seal coating.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<[See Annex I - To be completed nationally]> *[For referral procedures]*
{PRODUCT NAME} 40mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

Each {PRODUCT NAME} 40 mg film-coated tablet contains 131.22 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White elliptical, film-coated tablets debossed "40" on one side and "PD 157" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

{PRODUCT NAME} is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

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

Prevention of cardiovascular disease

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

4.2 Posology and method of administration

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

Dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.

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

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

For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatment goal is LDL-C < 3 mmol/l (or < 115 mg/dl) and total cholesterol < 5 mmol/l (or < 190 mg/dl).

Adapted from "Prevention of coronary heart disease in clinical practice:
Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention" in Atherosclerosis 140 (1998) 199-270.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with {PRODUCT NAME} 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

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

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

Prevention of cardiovascular disease

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

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations nor lipid effects of {PRODUCT NAME}; thus, no adjustment of dose is required.

Geriatric use

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

Pediatric use

Pediatric use should only be carried out by specialists.
Experience in pediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

{PRODUCT NAME} is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breast-feeding
- 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 transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of {PRODUCT NAME} is recommended (see section 4.8).

{PRODUCT NAME} should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle effects

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

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

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

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

Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Interaction may occur when {PRODUCT NAME} is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see section 4.4).

Inhibitors of P-glycoprotein

Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. ciclosporin) can increase the bioavailability of atorvastatin.

Erythromycin, clarithromycin

Coadministration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the Cmax and AUC of atorvastatin by 56% and 80% respectively.

Itraconazole

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 3-fold increase in atorvastatin AUC.

Protease inhibitors

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

Grapefruit juice

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

Inducers of cytochrome P450 3A4

The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on {PRODUCT NAME} is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other medicinal products with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.

Other concomitant therapy

Gemfibrozil / fibric acid derivatives
The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibric acid derivatives. According to results of in vitro studies the metabolic pathway of atorvastatin via glucuronidation is inhibited by Gemfibrozil. This may possibly lead to increased plasma levels of atorvastatin (see section 4.4).

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking digoxin should be monitored appropriately.

Oral contraceptives
Coadministration of {PRODUCT NAME} with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with {PRODUCT NAME}. However, lipid effects were greater when {PRODUCT NAME} and colestipol were coadministered than when either medicinal product was given alone.

Antacid
Coadministration of {PRODUCT NAME} with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approx. 35%; however, LDL-C reduction was not altered.

Warfarin
Coadministration of {PRODUCT NAME} and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of {PRODUCT NAME} treatment. Nevertheless, patients receiving warfarin should be closely monitored when {PRODUCT NAME} is added to their therapy.

Phenazone
Coadministration of multiple doses of {PRODUCT NAME} and phenazone showed little or no detectable effect in the clearance of phenazone.

Cimetidine
An interaction study with cimetidine and {PRODUCT NAME} was conducted, and no interaction was seen.

Amlodipine
Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Other
In clinical studies in which {PRODUCT NAME} was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

{PRODUCT NAME} is contraindicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

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

4.7 Effects on ability to drive and use machines

{PRODUCT NAME} has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Less than 2% of patients were discontinued from clinical trials due to side effects attributed to {PRODUCT NAME}.

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

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

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: anorexia, vomiting.

Blood and lymphatic system disorders

Uncommon: thrombocytopenia.

Immune system disorders

Common: allergic reactions.
Very rare: anaphylaxis.

Endocrine disorders

Uncommon: alopecia, hyperglycaemia, hypoglycaemia, pancreatitis.

Psychiatric

Common: insomnia.
Uncommon: amnesia.

Nervous system disorders

Common: headache, dizziness, paraesthaesia, hypoesthesia.
Uncommon: peripheral neuropathy.

Hepato-biliary disorders

Rare: hepatitis, cholestatic jaundice.

Skin/Appendages

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

Ear and Labyrinth Disorders

Uncommon: tinnitus

Musculoskeletal disorders

Common: myalgia, arthralgia.
Uncommon: myopathy.
Rare: myositis, rhabdomyolysis.

Reproductive system disorders

Uncommon: impotence.

General disorders

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

Investigations

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, ATC code: C10AA05

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet completed.

Atherosclerosis

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

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

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

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

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

Acute coronary syndrome

In the MIRACL study, atorvastatin 80 mg has been evaluated in 3,086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non Q-wave MI or unstable angina). Treatment was initiated during the acute phase after hospital admission and lasted for a period of 16 weeks. Treatment with atorvastatin 80 mg/day increased the time to occurrence of the combined primary endpoint, defined as death from any cause, nonfatal MI, resuscitated cardiac arrest, or angina pectoris with evidence of myocardial ischaemia requiring hospitalization, indicating a risk reduction by 16% (p=0.048). This was mainly due to a 26% reduction in re-hospitalisation for angina pectoris with

evidence of myocardial ischaemia (p=0.018). The other secondary endpoints did not reach statistical significance on their own (overall: Placebo: 22.2%, Atorvastatin: 22.4%).

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

Prevention of cardiovascular disease

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

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

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

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

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

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

Patients were treated with either atorvastatin 10 mg daily (n=1428) or placebo (n=1410) for a median follow-up of 3.9 years

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37%	83 vs. 127	3.2%	0.0010
MI (fatal and non-fatal AMI, silent MI)	42%	38 vs 64	1.9%	0.0070
Strokes (Fatal and non-fatal)	48%	21 vs. 39	1.3%	0.0163

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

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

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism

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

Excretion

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

Special populations

- Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: Pharmacokinetic data in the paediatric population are not available.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10% lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
- Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$. Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Polysorbate 80
Hyprolose
Magnesium stearate

Film coating

Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Talc
Simethicone
Stearate emulsifiers
Sorbic acid
Candelilla wax

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets.
Hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

The blisters consist of a forming film made of polyamide/aluminum foil/polyvinyl chloride and a backing made of either paper/polyester/aluminum foil/vinyl heat-seal coating or aluminum foil/vinyl heat-seal coating.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

<[See Annex I - To be completed nationally]> *[For referral procedures]*
{PRODUCT NAME} 80mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients:

Each {PRODUCT NAME} 80 mg film-coated tablet contains 262.44 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
White elliptical, film-coated tablets debossed "80" on one side and "PD 158" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia

{PRODUCT NAME} is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (Corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.

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

Prevention of cardiovascular disease

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

4.2 Posology and method of administration

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

Dosage should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response.

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

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

For patients with established coronary heart disease or other patients at increased risk of ischemic events, the treatment goal is LDL-C < 3 mmol/l (or < 115 mg/dl) and total cholesterol < 5 mmol/l (or < 190 mg/dl).

Adapted from "Prevention of coronary heart disease in clinical practice:
Recommendations of the Second Joint Task Force of European and Other Societies on Coronary Prevention" in Atherosclerosis 140 (1998) 199-270.

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

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

Heterozygous familial hypercholesterolaemia

Patients should be started with {PRODUCT NAME} 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

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

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

Prevention of cardiovascular disease

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

Dosage in patients with renal insufficiency

Renal disease has no influence on the atorvastatin plasma concentrations nor lipid effects of {PRODUCT NAME}; thus, no adjustment of dose is required.

Geriatric use

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

Pediatric use

Pediatric use should only be carried out by specialists.
Experience in pediatrics is limited to a small number of patients (age 4 - 17 years) with severe dyslipidemias, such as homozygous familial hypercholesterolemia. The recommended starting dose in this population is 10 mg of atorvastatin per day. The dose may be increased to 80 mg daily, according to the response and tolerability. Developmental safety data in this population have not been evaluated.

4.3 Contraindications

{PRODUCT NAME} is contraindicated in patients:
- with hypersensitivity to the active substance or to any of the excipients of this medication
- with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal
- with myopathy
- during pregnancy
- while breast-feeding
- 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 transaminases of greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of {PRODUCT NAME} is recommended (see section 4.8).

{PRODUCT NAME} should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Skeletal muscle effects

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

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

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

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

Whilst on treatment
- Patients must be asked to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivatives, macrolide antibiotics including erythromycin, azole antifungals, or niacin and on rare occasions has resulted in rhabdomyolysis with renal dysfunction secondary to myoglobinuria. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see section 4.4).

Inhibitors of cytochrome P450 3A4

Atorvastatin is metabolized by cytochrome P450 3A4. Interaction may occur when {PRODUCT NAME} is administered with inhibitors of cytochrome P450 3A4 (e.g. ciclosporin, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors). Concomitant administration can lead to increased plasma concentrations of atorvastatin. Therefore, special caution should be exercised when atorvastatin is used in combination with such medicinal agents (see section 4.4).

Inhibitors of P-glycoprotein

Atorvastatin and atorvastatin-metabolites are substrates of P-glycoprotein. Inhibitors of the P-glycoprotein (e.g. ciclosporin) can increase the bioavailability of atorvastatin.

Erythromycin, clarithromycin

Coadministration of atorvastatin 10 mg OD and erythromycin (500 mg QID), or atorvastatin 10 mg OD and clarithromycin (500 mg BID), known inhibitors of cytochrome P450 3A4, were associated with higher plasma concentrations of atorvastatin. Clarithromycin increased the C_{max} and AUC of atorvastatin by 56% and 80% respectively.

Itraconazole

Concomitant administration of atorvastatin 40 mg and itraconazole 200 mg daily resulted in a 3-fold increase in atorvastatin AUC.

Protease inhibitors

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

Grapefruit juice

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

Inducers of cytochrome P450 3A4

The effect of inducers of cytochrome P450 3A4 (e.g. rifampicin or phenytoin) on {PRODUCT NAME} is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other medicinal products with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.

Other concomitant therapy

Gemfibrozil / fibric acid derivatives
The risk of atorvastatin-induced myopathy may be increased with the concomitant use of fibric acid derivatives. According to results of in vitro studies the metabolic pathway of atorvastatin via glucuronidation is inhibited by Gemfibrozil. This may possibly lead to increased plasma levels of atorvastatin (see section 4.4).

Digoxin
When multiple doses of digoxin and 10 mg atorvastatin were coadministered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. This interaction may be explained by an inhibition of the membrane transport protein, P-glycoprotein. Patients taking digoxin should be monitored appropriately.

Oral contraceptives
Coadministration of {PRODUCT NAME} with an oral contraceptive produced increases in plasma concentrations of norethindrone and ethinyl oestradiol. These increased concentrations should be considered when selecting oral contraceptive doses.

Colestipol
Plasma concentrations of atorvastatin and its active metabolites were lower (by approx. 25%) when colestipol was coadministered with {PRODUCT NAME}. However, lipid effects were greater when {PRODUCT NAME} and colestipol were coadministered than when either medicinal products was given alone.

Antacid
Coadministration of {PRODUCT NAME} with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approx. 35%; however, LDL-C reduction was not altered.

Warfarin
Coadministration of {PRODUCT NAME} and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of {PRODUCT NAME} treatment. Nevertheless, patients receiving warfarin should be closely monitored when {PRODUCT NAME} is added to their therapy.

Phenazone
Coadministration of multiple doses of {PRODUCT NAME} and phenazone showed little or no detectable effect in the clearance of phenazone.

Cimetidine
An interaction study with cimetidine and {PRODUCT NAME} was conducted, and no interaction was seen.

Amlodipine
Atorvastatin pharmacokinetics were not altered by the coadministration of atorvastatin 80 mg and amlodipine 10 mg at steady state.

Other
In clinical studies in which {PRODUCT NAME} was administered with antihypertensives or hypoglycaemic agents no clinically significant interactions were seen.

4.6 Pregnancy and lactation

{PRODUCT NAME} is contraindicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of atorvastatin in pregnancy and lactation has not yet been proven.

There is evidence from animal studies that HMG-CoA reductase inhibitors may influence the development of embryos or foetuses. The development of rat offspring was delayed and post-natal survival reduced during exposure of the dams to atorvastatin at doses above 20 mg/kg/day (the clinical systemic exposure).

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

4.7 Effects on ability to drive and use machines

{PRODUCT NAME} has negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

Less than 2% of patients were discontinued from clinical trials due to side effects attributed to {PRODUCT NAME}.

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

Estimated frequencies of events are ranked according to the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000 < 1/100); rare (≥ 1/10,00, < 1/1,000); very rare (≤ 1/10,000).

Gastrointestinal disorders

Common: constipation, flatulence, dyspepsia, nausea, diarrhoea.
Uncommon: anorexia, vomiting.

Blood and lymphatic system disorders

Uncommon: thrombocytopenia.

Immune system disorders

Common: allergic reactions.
Very rare: anaphylaxis.

Endocrine disorders

Uncommon: alopecia, hyperglycaemia, hypoglycaemia, pancreatitis.

Psychiatric

Common: insomnia.
Uncommon: amnesia.

Nervous system disorders

Common: headache, dizziness, paraesthaesia, hypoesthesia.
Uncommon: peripheral neuropathy.

Hepato-biliary disorders

Rare: hepatitis, cholestatic jaundice.

Skin/Appendages

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

Ear and Labyrinth Disorders

Uncommon: tinnitus

Musculoskeletal disorders

Common: myalgia, arthralgia.
Uncommon: myopathy.
Rare: myositis, rhabdomyolysis.

Reproductive system disorders

Uncommon: impotence.

General disorders

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

Investigations

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

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA-reductase inhibitors, ATC code: C10AA05

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

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

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

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

Reductions in total-C, LDL-C, and apolipoprotein B have been proven to reduce risk for cardiovascular events and cardiovascular mortality. Mortality and morbidity studies with atorvastatin have not yet completed.

Atherosclerosis

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

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

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

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

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

Acute coronary syndrome

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

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

Prevention of cardiovascular disease

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

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

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

Event	Relative Risk Reduction (%)	No. of Events (Atorvastatin vs Placebo)	Absolute Risk Reduction[1] (%)	p-value
Fatal CHD plus non-fatal MI	36%	100 vs. 154	1.1%	0.0005
Total cardiovascular events and revascularization procedures	20%	389 vs. 483	1.9%	0.0008
Total coronary events	29%	178 vs 247	1.4%	0.0006

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

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

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

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

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

	Relative Risk	No. of Events (Atorvastatin	Absolute Risk

Event	Reduction (%)	vs Placebo)	Reduction[1] (%)	p-value
Major cardiovascular events (fatal and non-fatal AMI, silent MI, acute CHD death, unstable angina, CABG, PTCA, revascularization, stroke)	37 %	83 vs. 127	3.2 %	0.0010
MI (fatal and non-fatal AMI, silent MI)	42 %	38 vs 64	1.9 %	0.0070
Strokes (Fatal and non-fatal)	48 %	21 vs. 39	1.3 %	0.0163

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

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

5.2 Pharmacokinetic properties

Absorption

Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations (C_{max}) occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. After oral administration, atorvastatin film-coated tablets are 95% to 99% bioavailable compared to the oral solution. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is ≥ 98% bound to plasma proteins.

Metabolism

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

Excretion

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

Special populations

- Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.
- Paediatric: Pharmacokinetic data in the paediatric population are not available.
- Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: approx. 20% higher for C_{max} and approx. 10 % lower for AUC). These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
- Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
- Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3 Preclinical safety data

Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on $AUC_{(0-24)}$ values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on $AUC_{(0-24)}$. Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 in vitro tests with and without metabolic activation and in 1 in vivo assay. In animal studies atorvastatin had no effect on male or female fertility at doses up to 175 and 225 mg/kg/day, respectively, and was not teratogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carbonate
Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Polysorbate 80
Hyprolose
Magnesium stearate

Film coating

Hypromellose
Polyethylene glycol
Titanium dioxide (E171)
Talc
Simethicone
Stearate emulsifiers
Sorbic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

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 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets.
Hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

The blisters consist of a forming film made of polyamide/aluminum foil/polyvinyl chloride and a backing made of either paper/polyester/aluminum foil/vinyl heat-seal coating or aluminum foil/vinyl heat-seal coating.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>

<[See Annex I - To be completed nationally]> *[For referral procedures]*

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

<[To be completed nationally]>

10. DATE OF REVISION OF THE TEXT

LABELLING AND PACKAGE LEAFLET

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK CARTON (for blisters of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 tablets)
HOSPITAL PACK LABEL (for blisters of 200 & 500 tablets)

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 10 mg Film-coated tablets
Atorvastatin calcium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 10 mg atorvastatin (as calcium salt trihydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.

4 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
84 tablets
98 tablets
100 tablets
200 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use only.

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

Keep out of the reach and sight of children.
Use as directed by your doctor.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed for your protection.
Do not use, if package has already been opened.

8. EXPIRY DATE

EXP:

Batch/ EXP: see individual pack (label for sticker for hospital packs only)

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{PRODUCT NAME} 10 mg Film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 10 mg Film-coated tablets
Atorvastatin calcium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name}

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

{for blisters of 7 tablets – the abbreviated days of the week may be printed on the foil for each tablet i.e. MON, TUE, WED, THU, FRI, SAT, SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK CARTON (for blisters of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 tablets)
HOSPITAL PACK LABEL (for blisters of 200 & 500 tablets)

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 20 mg Film-coated tablets
Atorvastatin calcium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 20 mg atorvastatin (as calcium salt trihydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.

4 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
84 tablets
98 tablets
100 tablets
200 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use only.

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

Keep out of the reach and sight of children.
Use as directed by your doctor.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed for your protection.
Do not use, if package has already been opened.

8. EXPIRY DATE

EXP:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{PRODUCT NAME} 20 mg Film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 20 mg Film-coated tablets
Atorvastatin calcium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name}

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. OTHER

{for blisters of 7 tablets – the abbreviated days of the week may be printed on the foil for each tablet
i.e. MON, TUE, WED, THU, FRI, SAT, SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK CARTON (for blisters of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 tablets)
HOSPITAL PACK LABEL (for blisters of 200 & 500 tablets)

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 40 mg Film-coated tablets
Atorvastatin calcium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 40 mg atorvastatin (as calcium salt trihydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.

4 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
84 tablets
98 tablets
100 tablets
200 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use only.

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

Keep out of the reach and sight of children.
Use as directed by your doctor.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed for your protection.
Do not use, if package has already been opened.

8. EXPIRY DATE

EXP:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{PRODUCT NAME} 40 mg Film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 40 mg Film-coated tablets
Atorvastatin calcium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name}

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch :

5. OTHER

{for blisters of 7 tablets – the abbreviated days of the week may be printed on the foil for each tablet i.e. MON, TUE, WED, THU, FRI, SAT, SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER PACK CARTON (for blisters of 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98, 100 tablets)
HOSPITAL PACK LABEL (for blisters of 200 & 500 tablets)

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 80 mg Film-coated tablets
Atorvastatin calcium

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 film-coated tablet contains 80 mg atorvastatin (as calcium salt trihydrate).

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets.

4 tablets
7 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
56 tablets
84 tablets
98 tablets
100 tablets
200 tablets
500 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use only.

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

Keep out of the reach and sight of children.
Use as directed by your doctor.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Sealed for your protection.
Do not use, if package has already been opened.

8. EXPIRY DATE

EXP:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Batch:

Batch / EXP: see individual pack (label for sticker for hospital packs only)

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{PRODUCT NAME} 80 mg Film-coated tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

{PRODUCT NAME} 80 mg Film-coated tablets
Atorvastatin calcium

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<[To be completed nationally]>
{Name}

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch :

5. OTHER

{for blisters of 7 tablets – the abbreviated days of the week may be printed on the foil for each tablet i.e. MON, TUE, WED, THU, FRI, SAT, SUN

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

{PRODUCT NAME} 10 mg film-coated tablets
Atorvastatin calcium
<[See Annex I - To be completed nationally]> *[For referral procedures]*

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

In this leaflet:

1. WHAT {PRODUCT NAME} 10 mg IS AND WHAT IT IS USED FOR

{PRODUCT NAME} belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

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

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

2. BEFORE YOU TAKE {PRODUCT NAME} 10 mg

Do not take {PRODUCT NAME} 10 mg
- if you are hypersensitive (allergic) to {PRODUCT NAME} or to any similar medicines used to lower blood lipids or to any of the other 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 are a woman able to have children and not using reliable contraception
- if you are pregnant, trying to become pregnant or breast-feeding
- if you have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains)

Take special care with {PRODUCT NAME} 10 mg
The following are reasons why {PRODUCT NAME} may not be suitable for you:
- If you have kidney problems

- If you have an under-active thyroid gland (hypothyroidism)
- If you have had repeated or unexplained muscle aches or pains, a personnal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)
- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

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

Taking other medicines
There are some medicines that may interact with {PRODUCT NAME}:
- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole; rifampicin
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid derivatives, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. nifedipine; medicines to regulate your heart rhythm e.g. digoxin
- Some benzodiazepines used for anxiety and other conditions, e.g. nefazodone
- Protease inhibitors used in the treatment of HIV
- Other medicines known to interact with {PRODUCT NAME} include warfarin (which reduces blood clotting), oral contraceptives, phenytoin (an anti-convulsant for epilepsy), and antacids (indigestion products containing aluminium or magnesium)

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 {PRODUCT NAME} 10 mg with food and drink
Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of {PRODUCT}.

Alcohol
Avoid drinking too much alcohol while taking this medicine. See Section 2 "Take special care with {PRODUCT NAME} 10 mg" for details

Pregnancy
Do not take {PRODUCT NAME} if you are pregnant, if you think you may be pregnant, or if you are trying to become pregnant. Women of child-bearing age must take appropriate contraceptive measures.
Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Do not take {PRODUCT NAME} if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

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

3. HOW TO TAKE {PRODUCT NAME} 10 mg

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

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

Always take {PRODUCT NAME} 10 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {PRODUCT NAME} 10 mg.

The duration of treatment with {PRODUCT NAME} 10 mg is determined by your doctor.

Please ask your doctor if you think that the effect of {PRODUCT NAME} 10 mg is too strong or too weak.

If you take more {PRODUCT NAME} 10 mg than you should
If you accidently take too many {PRODUCT NAME} tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take {PRODUCT NAME} 10 mg
If you forget to take a dose, just take your next scheduled dose at the correct time.
Do not take a double dose to make up for a forgotten dose.

If you stop taking {PRODUCT NAME} 10 mg
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {PRODUCT NAME} 10 mg can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 {PRODUCT NAME} and tell your doctor immediately.*

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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 {PRODUCT NAME}:
As with all medicines, {PRODUCT NAME} can sometimes cause side effects in some individuals. Common conditions, affect at least 100 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients, up to 9,900 are not expected to have these side effects).
These include:

- Nausea; abdominal pain, constipation, wind, indigestion, headache, muscle pain, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions, numbness, joint pain and back pain, asthenia, peripheral oedema, itching.

Other less common side effects have been seen in some patients taking {PRODUCT NAME} 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 {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,900 are not expected to have these side effects).
These include:

- Anorexia (loss of appetite), numbness or tingling in the fingers and toes, vomiting, rash, muscle cramps, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, hives, feeling unwell, impotence, hair loss, pancreatitis (inflammation of the pancreas leading to stomach pain).

Rare conditions affect fewer than 10 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,990 are not expected to have these side effects).
These include:

- Reductions in sensation of skin to light touch or pain, muscle tenderness, blistering rash, peripheral oedema (e.g. ankle swelling), hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes), rhabdomyolysis (serious muscle pain and weakness, often associated with fever).

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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). Increases and decreases in blood sugar levels have also been seen (If you have diabetes you should continue careful monitoring of your blood sugar levels).

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

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

5. HOW TO STORE {PRODUCT NAME} 10 mg

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use {PRODUCT NAME} 10 mg after the expiry date {Exp. Date:} which is stated on the container and outer packaging. The expiry date refers to the last day of that month.

Do not use {PRODUCT NAME} 10 mg if you notice visible signs of deterioration.

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

6. FURTHER INFORMATION

What {PRODUCT NAME} 10 mg contains
The active substance of {PRODUCT NAME} is atorvastatin. Each tablet contains 10 mg of atorvastatin as atorvastatin calcium trihydrate.

{PRODUCT NAME} tablets also contain the inactive ingredients: calcium carbonate, microcrystalline cellulose, lactose, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose and magnesium stearate.

The coating of {PRODUCT NAME}contains hypromellose, macrogol 8000, titanium dioxide (E171), talc, simeticone, macrogol stearate, sorbic acid and candelilla wax.

What {PRODUCT NAME} 10 mg looks like and contents of the pack
{PRODUCT NAME} film-coated tablets are white with an oval shape. They are marked with 10 on one side and PD155 on the other side.

{PRODUCT NAME} 10 mg are available in blister packs containing 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets and hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

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

Austria	Sortis
Belgium	Lipitor
Denmark	Zarator
Finland	Lipitor
Germany	Sortis
Greece	Lipitor
Italy	Xarator
Luxembourg	Lipitor
Portugal	Zarator
The Netherlands	Lipitor
Spain	Zarator
Sweden	Lipitor

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

{PRODUCT NAME} 20 mg film-coated tablets
Atorvastatin calcium
<[See Annex I - To be completed nationally]> *[For referral procedures]*

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

In this leaflet:

1. WHAT {PRODUCT NAME} 20 mg IS AND WHAT IT IS USED FOR

{PRODUCT NAME} belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

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

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

2. BEFORE YOU TAKE {PRODUCT NAME} 20 mg

Do not take {PRODUCT NAME} 20 mg
if you are hypersensitive (allergic) to {PRODUCT NAME} or to any similar medicines used to lower blood lipids or to any of the other 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 are a woman able to have children and not using reliable contraception
- if you are pregnant, trying to become pregnant or breast-feeding
- if you have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains)

Take special care with {PRODUCT NAME} 20 mg
The following are reasons why {PRODUCT NAME} may not be suitable for you:
- If you have kidney problems

- If you have an under-active thyroid gland (hypothyroidism)
- If you have had repeated or unexplained muscle aches or pains, a personnal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)
- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

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

Taking other medicines
There are some medicines that may interact with {PRODUCT NAME}:
- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole; rifampicin
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid derivatives, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. nifedipine; medicines to regulate your heart rhythm e.g. digoxin
- Some benzodiazepines used for anxiety and other conditions, e.g. nefazodone
- Protease inhibitors used in the treatment of HIV
- Other medicines known to interact with {PRODUCT NAME} include warfarin (which reduces blood clotting), oral contraceptives, phenytoin (an anti-convulsant for epilepsy), and antacids (indigestion products containing aluminium or magnesium)

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 {PRODUCT NAME} 20 mg with food and drink
Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of {PRODUCT}.

Alcohol
See Section 2 "Take special care with {PRODUCT NAME} 20 mg" for details.
Avoid drinking too much alcohol while taking this medicine.

Pregnancy
Do not take {PRODUCT NAME} if you are pregnant, if you think you may be pregnant, or if you are trying to become pregnant. Women of child-bearing age must take appropriate contraceptive measures.
Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Do not take {PRODUCT NAME} if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

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

3. HOW TO TAKE {PRODUCT NAME} 20 mg

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

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

Always take {PRODUCT NAME} 20 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {PRODUCT NAME} 20 mg.

The duration of treatment with {PRODUCT NAME} 20 mg is determined by your doctor.

Please ask your doctor if you think that the effect of {PRODUCT NAME} 20 mg is too strong or too weak.

If you take more {PRODUCT NAME} 20 mg than you should
If you accidently take too many {PRODUCT NAME} tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take {PRODUCT NAME} 20 mg
If you forget to take a dose, just take your next scheduled dose at the correct time.

If you stop taking {PRODUCT NAME} 20 mg
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {PRODUCT NAME} 20 mg can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 {PRODUCT NAME} and tell your doctor immediately.*

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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 {PRODUCT NAME}:

As with all medicines, {PRODUCT NAME} can sometimes cause side effects in some individuals. Common conditions, affect at least 100 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients, up to 9,900 are not expected to have these side effects).
These include:

- Nausea; abdominal pain, constipation, wind, indigestion, headache, muscle pain, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions, numbness, joint pain and back pain, asthenia, peripheral oedema, itching.

Other less common side effects have been seen in some patients taking {PRODUCT NAME} 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 {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,900 are not expected to have these side effects).
These include:

- Anorexia (loss of appetite), numbness or tingling in the fingers and toes, vomiting, rash, muscle cramps, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, hives, feeling unwell, impotence, hair loss, pancreatitis (inflammation of the pancreas leading to stomach pain).

Rare conditions affect fewer than 10 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,990 are not expected to have these side effects).
These include:

- Reductions in sensation of skin to light touch or pain, muscle tenderness, blistering rash, peripheral oedema (e.g. ankle swelling), hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes), rhabdomyolysis (serious muscle pain and weakness, often associated with fever).

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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). Increases and decreases in blood sugar levels have also been seen (If you have diabetes you should continue careful monitoring of your blood sugar levels).

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

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

5. HOW TO STORE {PRODUCT NAME} 20 mg

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use {PRODUCT NAME} 20 mg after the expiry date {Exp. Date:} which is stated on the container and outer packaging. The expiry date refers to the last day of that month.

Do not use {PRODUCT NAME} 20 mg if you notice visible signs of deterioration.

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

6. FURTHER INFORMATION

What {PRODUCT NAME} 20 mg contains
The active substance of {PRODUCT NAME} is atorvastatin. Each tablet contains 20 mg of atorvastatin as atorvastatin calcium trihydrate.

{PRODUCT NAME} tablets also contain the inactive ingredients: calcium carbonate, microcrystalline cellulose, lactose, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose and magnesium stearate.

The coating of {PRODUCT NAME} contains hypromellose, macrogol 8000, titanium dioxide (E171), talc, simeticone, macrogol stearate, sorbic acid and candelilla wax.

What {PRODUCT NAME} 20 mg looks like and contents of the pack
{PRODUCT NAME} film-coated tablets are white with an oval shape. They are marked with 20 on one side and PD156 on the other side.

{PRODUCT NAME} 20 mg are available in blister packs containing 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets and hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

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

Austria	Sortis
Belgium	Lipitor
Denmark	Zarator
Finland	Lipitor
Germany	Sortis
Greece	Lipitor
Italy	Xarator
Luxembourg	Lipitor
Portugal	Zarator
The Netherlands	Lipitor
Spain	Zarator
Sweden	Lipitor

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

{PRODUCT NAME} 40 mg film-coated tablets
Atorvastatin calcium
<[See Annex I - To be completed nationally]> *[For referral procedures]*

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

In this leaflet:

1. WHAT {PRODUCT NAME} 40 mg IS AND WHAT IT IS USED FOR

{PRODUCT NAME} belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

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

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

2. BEFORE YOU TAKE {PRODUCT NAME} 40 mg

Do not take {PRODUCT NAME} 40 mg
- if you are hypersensitive (allergic) to {PRODUCT NAME} or to any similar medicines used to lower blood lipids or to any of the other 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 are a woman able to have children and not using reliable contraception
- if you are pregnant, trying to become pregnant or breast-feeding
- if you have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains)

Take special care with {PRODUCT NAME} 40 mg
The following are reasons why {PRODUCT NAME} may not be suitable for you:
- If you have kidney problems
- If you have an under-active thyroid gland (hypothyroidism)

- If you have had repeated or unexplained muscle aches or pains, a personnal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)
- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

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

Taking other medicines
There are some medicines that may interact with {PRODUCT NAME}:
- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole; rifampicin
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid derivatives, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. nifedipine; medicines to regulate your heart rhythm e.g. digoxin
- Some benzodiazepines used for anxiety and other conditions, e.g. nefazodone
- Protease inhibitors used in the treatment of HIV
- Other medicines known to interact with {PRODUCT NAME} include warfarin (which reduces blood clotting), oral contraceptives, phenytoin (an anti-convulsant for epilepsy), and antacids (indigestion products containing aluminium or magnesium)

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 {PRODUCT NAME} 40 mg with food and drink
Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of {PRODUCT}.

Alcohol
Avoid drinking too much alcohol while taking this medicine. See Section 2 "Take special care with {PRODUCT NAME} 40 mg" for details

Pregnancy
Do not take {PRODUCT NAME} if you are pregnant, if you think you may be pregnant, or if you are trying to become pregnant. Women of child-bearing age must take appropriate measures.
Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Do not take {PRODUCT NAME} if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

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

3. HOW TO TAKE {PRODUCT NAME} 40 mg

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

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

Always take {PRODUCT NAME} 40 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {PRODUCT NAME} 40 mg.

The duration of treatment with {PRODUCT NAME} 40 mg is determined by your doctor.

Please ask your doctor if you think that the effect of {PRODUCT NAME} 40 mg is too strong or too weak.

If you take more {PRODUCT NAME} 40 mg than you should
If you accidently take too many {PRODUCT NAME} tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take {PRODUCT NAME} 40 mg
If you forget to take a dose, just take your next scheduled dose at the correct time.

If you stop taking {PRODUCT NAME} 40 mg
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {PRODUCT NAME} 40 mg can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 {PRODUCT NAME} and tell your doctor immediately.*

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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 {PRODUCT NAME}:

As with all medicines, {PRODUCT NAME} can sometimes cause side effects in some individuals. Common conditions, affect at least 100 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients, up to 9,900 are not expected to have these side effects).
These include:

- Nausea; abdominal pain, constipation, wind, indigestion, headache, muscle pain, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions, numbness, joint pain and back pain, asthenia, peripheral oedema, itching.

Other less common side effects have been seen in some patients taking {PRODUCT NAME} 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 {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,900 are not expected to have these side effects).
These include:

- Anorexia (loss of appetite), numbness or tingling in the fingers and toes, vomiting, rash, muscle cramps, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, hives, feeling unwell, impotence, hair loss, pancreatitis (inflammation of the pancreas leading to stomach pain).

Rare conditions affect fewer than 10 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,990 are not expected to have these side effects).
These include:

- Reductions in sensation of skin to light touch or pain, muscle tenderness, blistering rash, peripheral oedema (e.g. ankle swelling), hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes), rhabdomyolysis (serious muscle pain and weakness, often associated with fever).

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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). Increases and decreases in blood sugar levels have also been seen (If you have diabetes you should continue careful monitoring of your blood sugar levels).

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

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

5. HOW TO STORE {PRODUCT NAME} 40 mg

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use {PRODUCT NAME} 40 mg after the expiry date {Exp. Date:} which is stated on the container and outer packaging. The expiry date refers to the last day of that month.

Do not use {PRODUCT NAME} 40 mg if you notice visible signs of deterioration.

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

6. FURTHER INFORMATION

What {PRODUCT NAME} 40 mg contains
The active substance of {PRODUCT NAME} is atorvastatin. Each tablet contains 40 mg of atorvastatin as atorvastatin calcium trihydrate.

{PRODUCT NAME} tablets also contain the inactive ingredients: calcium carbonate, microcrystalline cellulose, lactose, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose and magnesium stearate.

The coating of {PRODUCT NAME} contains hypromellose, macrogol 8000, titanium dioxide (E171), talc, simeticone, macrogol stearate, sorbic acid and candelilla wax.

What {PRODUCT NAME} 40 mg looks like and contents of the pack
{PRODUCT NAME} film-coated tablets are white with an oval shape. They are marked with 40 on one side and PD157 on the other side.

{PRODUCT NAME} 40 mg are available in blister packs containing 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets and hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

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

Austria	Sortis
Belgium	Lipitor
Denmark	Zarator
Finland	Lipitor
Germany	Sortis
Greece	Lipitor
Italy	Xarator
Luxembourg	Lipitor
Portugal	Zarator
The Netherlands	Lipitor
Spain	Zarator
Sweden	Lipitor

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>

PACKAGE LEAFLET: INFORMATION FOR THE USER

{PRODUCT NAME} 80 mg film-coated tablets
Atorvastatin calcium
<[See Annex I - To be completed nationally]> *[For referral procedures]*

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

In this leaflet:

1. WHAT {PRODUCT NAME} 80 mg IS AND WHAT IT IS USED FOR

{PRODUCT NAME} belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

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

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

2. BEFORE YOU TAKE {PRODUCT NAME} 80 mg

Do not take {PRODUCT NAME} 80 mg
- if you are hypersensitive (allergic) to {PRODUCT NAME} or to any similar medicines used to lower blood lipids or to any of the other 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 are a woman able to have children and not using reliable contraception
- if you are pregnant, trying to become pregnant or breast-feeding
- if you have a muscle disorder called myopathy (repeated or unexplained muscle aches or pains)

Take special care with {PRODUCT NAME} 80 mg
The following are reasons why {PRODUCT NAME} may not be suitable for you:
- If you have kidney problems

- If you have an under-active thyroid gland (hypothyroidism)
- If you have had repeated or unexplained muscle aches or pains, a personnal history or family history of muscle problems
- If you have had previous muscular problems during treatment with other lipid-lowering medicines (e.g. other '-statin' or '-fibrate' medicines)
- If you regularly drink a large amount of alcohol
- If you have a history of liver disease
- If you are older than 70 years
- If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

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

Taking other medicines
There are some medicines that may interact with {PRODUCT NAME}:
- Medicines used to alter the way your immune system works, e.g. ciclosporin
- Certain antibiotics or antifungal medicines, e.g. erythromycin, clarithromycin, ketoconazole, itraconazole; rifampicin
- Other medicines to regulate lipid levels, e.g. gemfibrozil, other fibrates, nicotinic acid derivatives, colestipol
- Some calcium channel blockers used for angina or high blood pressure, e.g. nifedipine; medicines to regulate your heart rhythm e.g. digoxin
- Some benzodiazepines used for anxiety and other conditions, e.g. nefazodone
- Protease inhibitors used in the treatment of HIV e.g. nelfinavir
- Other medicines known to interact with {PRODUCT NAME} include warfarin (which reduces blood clotting), oral contraceptives, phenytoin (an anti-convulsant for epilepsy), and antacids (indigestion products containing aluminium or magnesium)

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 {PRODUCT NAME} 80 mg with food and drink
Grapefruit juice
Do not take more than one or two small glasses of grapefruit juice per day because large quantities of grapefruit juice can change the effects of {PRODUCT}.

Alcohol
Avoid drinking too much alcohol while taking this medicine. See Section 2 "Take special care with {PRODUCT NAME} 80 mg" for details.

Pregnancy
Do not take {PRODUCT NAME} if you are pregnant, if you think you may be pregnant, or if you are trying to become pregnant. Women of child-bearing age must take appropriate contraceptive measures.
Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding
Do not take {PRODUCT NAME} if you are breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

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

3. HOW TO TAKE {PRODUCT NAME} 80 mg

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

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

Always take {PRODUCT NAME} 80 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor will place you on a low-cholesterol diet, which you should maintain also during therapy with {PRODUCT NAME} 80 mg.

The duration of treatment with {PRODUCT NAME} 80 mg is determined by your doctor.

Please ask your doctor if you think that the effect of {PRODUCT NAME} 80 mg is too strong or too weak.

If you take more {PRODUCT NAME} 80 mg than you should
If you accidently take too many {PRODUCT NAME} tablets (more than your usual daily dose), contact your doctor or nearest hospital for advice.

If you forget to take {PRODUCT NAME} 80 mg
If you forget to take a dose, just take your next scheduled dose at the correct time.

If you stop taking {PRODUCT NAME} 80 mg
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, {PRODUCT NAME} 80 mg can cause side effects, although not everybody gets them. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

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 {PRODUCT NAME} and tell your doctor immediately.*

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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 {PRODUCT NAME}:

As with all medicines, {PRODUCT NAME} can sometimes cause side effects in some individuals. Common conditions, affect at least 100 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients, up to 9,900 are not expected to have these side effects).
These include:

- Nausea, abdominal pain, constipation, wind, indigestion, headache, muscle pain, weakness, diarrhoea, insomnia, dizziness, chest pain, allergic reactions, numbness, joint pain and back pain, asthenia, peripheral oedema, itching.

Other less common side effects have been seen in some patients taking {PRODUCT NAME} 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 {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,900 are not expected to have these side effects).
These include:

- Anorexia (loss of appetite), numbness or tingling in the fingers and toes, vomiting, rash, muscle cramps, unexpected bleeding or bruising, ringing in the ears and/or head, weight gain, loss of memory, hives, feeling unwell, impotence, hair loss, pancreatitis (inflammation of the pancreas leading to stomach pain).

Rare conditions affect fewer than 10 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, at least 9,990 are not expected to have these side effects).
These include:

- Reductions in sensation of skin to light touch or pain, muscle tenderness, blistering rash, peripheral oedema (e.g. ankle swelling), hepatitis (liver inflammation), jaundice (yellowing of the skin and whites of the eyes), rhabdomyolysis (serious muscle pain and weakness, often associated with fever).

Very rare conditions affect fewer than 1 in 10,000 patients taking {PRODUCT NAME} (this means that for every 10,000 patients taking {PRODUCT NAME}, 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). Increases and decreases in blood sugar levels have also been seen (If you have diabetes you should continue careful monitoring of your blood sugar levels).

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

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

5. HOW TO STORE {PRODUCT NAME} 80 mg

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.

Do not use {PRODUCT NAME} 80 mg after the expiry date {Exp. Date:} which is stated on the container and outer packaging. The expiry date refers to the last day of that month.

Do not use {PRODUCT NAME} 80 mg if you notice visible signs of deterioration.

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

6. FURTHER INFORMATION

What {PRODUCT NAME} 80 mg contains
The active substance of {PRODUCT NAME} is atorvastatin. Each tablet contains 80 mg of atorvastatin as atorvastatin calcium trihydrate.

{PRODUCT NAME} tablets also contain the inactive ingredients: calcium carbonate, microcrystalline cellulose, lactose, croscarmellose sodium, polysorbate 80, hydroxypropyl cellulose and magnesium stearate.

The coating of {PRODUCT NAME} contains hypromellose, macrogol 8000, titanium dioxide (E171), talc, simeticone, macrogol stearate and sorbic acid.

What {PRODUCT NAME} 80 mg looks like and contents of the pack
{PRODUCT NAME} film-coated tablets are white with an oval shape. They are marked with 80 on one side and PD158 on the other side.

{PRODUCT NAME} 80 mg are available in blister packs containing 4, 7, 10, 14, 20, 28, 30, 50, 56, 84, 98 and 100 film-coated tablets and hospital packs containing 200 (10 x 20) or 500 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

<[See Annex I - To be completed nationally]> *[For referral procedures, as appropriate]*

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

Austria	Sortis
Belgium	Lipitor
Denmark	Zarator
Finland	Lipitor
Germany	Sortis
Greece	Lipitor
Italy	Xarator
Luxembourg	Lipitor
Portugal	Zarator
The Netherlands	Lipitor
Spain	Zarator
Sweden	Lipitor

This leaflet was last approved in {MM/YYYY}.

<[To be completed nationally]>