SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Atorcor 10 mg film-coated tablets
Atorcor 20 mg film-coated tablets
Atorcor 40 mg film-coated tablets
Atorcor 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Atorcor 10 mg film-coated tablets
Each film-coated tablet contains:
Atorvastatin (calcium) …….. 10 mg

Atorcor 20 mg film-coated tablets
Each film-coated tablet contains:
Atorvastatin (calcium) …….. 20 mg

Atorcor 40 mg fim-coated tablets
Each film-coated tablet contains:
Atorvastatin (calcium) …….. 40 mg

Atorcor 80 mg film-coated tablets
Each film-coated tablet contains:
Atorvastatin (calcium) …….. 80 mg

Excipients with known effect:
Atorcor 10 mg film-coated tablets contain:
Lactose monohydrate…….64.0 mg

Atorcor 20 mg film-coated tablets contain:
Lactose monohydrate…… 128.0 mg

Atorcor 40 mg film-coated tablets contain:
Lactose monohydrate…… 256.0 mg

Atorcor 80 mg film-coated tablets contain:
Lactose monohydrate…… 512.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.
Atorvastatin 10 mg, 20 mg and 40 mg: Cylindrical, biconvex, scored, white-coloured tablets.
Atorvastatin 80 mg: Oblong, biconvex, scored, white-coloured tablets.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolaemia:

Atorcor is indicated, as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL cholesterol (LDL-C), apolipoprotein B and triglycerides in patients with primary hypercholesterolaemia, including heterozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures are inadequate.

Atorcor is also indicated to reduce total cholesterol and LDL cholesterol in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid lowering treatment (e.g. LDL aphaeresis) or when these treatments are not available.

Preventing heart disease:

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

4.2 Posology and method of administration

Posology

Before receiving **Atorcor**, patients should be place on a standard cholesterol-lowering diet, which should continue during the treatment.

Doses should be individualised according to baseline LDL cholesterol levels, the goal of therapy and patient response.

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

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

Most patients can be controlled with **Atorcor 10 mg** taken 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 **Atorcor** 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, doses may be increased up to a maximum of 80 mg daily, or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

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

Prevention of cardiovascular disease

The daily dose of atorvastatin in primary prevention trials is 10 mg. Higher doses may be necessary in order to attain LDL cholesterol levels in accordance with current guidelines.

Renal impairment

No adjustment of dose is required (see section 4.4)

Hepatic impairment

Atorcor should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). **Atorcor** is contraindicated in patients with active liver disease (see section 4.3).

Use in the elderly

At the recommended doses, efficacy and safety rates in patients over 70 are similar to those seen in the general population.

Paediatric use

Paediatric use should only be carried out by specialists.

Experience in paediatrics is limited to a small number of patients aged 4-17 with severe dyslipidaemia, such as homozygous familial hyperlipidaemia. In this population, the recommended starting dose is 10 mg of atorvastatin per day. Depending on response and tolerance, the dose may be increased to 80 mg daily. Developmental safety data in this population have not been evaluated.

Method of administration

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

4.3 Contraindications

Atorcor is contraindicated:

- With hypersensitivity to the active substance or to any of the excipients of this medicinal product;
- with active liver disease or unexplained persistent elevations of serum transaminase exceeding 3 times the upper limit of normal;
- During pregnancy, while breast-feeding and in women of child-bearing potential not using appropriate contraceptive measures (see section 4.6).

4.4 Special warnings and precautions for use

Liver effects

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

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

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL):

A post-hoc analysis of stroke sub-types in patients without coronary heart disease (CHD) having suffered a recent stroke or transient ischaemic attack (TIA) there was a higher incidence of haemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to the placebo group. This increased risk was observed particularly in patients with prior haemorrhagic stroke or lacunar infarct at study entry. For patients with prior haemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of haemorrhagic stroke should be considered carefully before initiating treatment (see section 5.1).

Skeletal muscle effects

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

Before the treatment

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

- Renal impairment.
- Hypothyroidism.
- A 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 the elderly (over 70), the necessity of such measurement should be considered, according to the presence of other predisposing factors for rhabdomyolysis.
- Situations where an increase in plasma levels may occur, such as interactions (see section 4.5) and special populations including genetic subpopulations (see section 5.2).

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

Creatine kinase measurement

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of any plausible alternative cause of CK increase as this makes value interpretation difficult. If CK levels are significantly elevated at baseline (> 5 times ULN), levels should be remeasured within 5-7 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 fever or malaise.
- If these symptoms occur whilst a patient is receiving treatment with atorvastatin, their CK levels must be measured. If these levels are significantly elevated (> 5 ULN), treatment should be stopped.
- If muscular symptoms are severe and cause daily discomfort, even if the CK levels are elevated to ≤ 5 x ULN, treatment discontinuation should be considered.
- If the symptoms disappear and CK levels return to normal, the re-introduction of atorvastatin or introduction of an alternative statin may be considered at the lowest dose and with close monitoring.
- Treatment with atorvastatin should be discontinued in the event of a clinically significant elevation of CK levels (> 10 times ULN) or if rhabdomyolysis is diagnosed or suspected.

Concomitant treatment with other medicinal products

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

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

The concurrent use of atorvastatin and fusidic acid is not recommended, therefore, temporary suspension of atorvastatin may be considered during fusidic acid therapy (see section 4.5)

Interstitial lung disease

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

Excipients

This medicinal product contains lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (seen in some populations of Lapland) or glucose or galactose absorption problems, should not use this medication.

This medicinal product contains sucrose. Patients with hereditary intolerance to fructose, glucose or galactose absorption problems, or sucrose-isomaltase deficiency must not use this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of co-administered medicinal products on atorvastatin

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

Cytochrome P450 3A4 inhibitors:

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

Moderate CYP3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil and fluconazole) may increase plasma concentrations of atorvastatin (see Table 1).. An increased risk of myopathy has been observed with the use of erythromycin in combination with statins. Interaction studies evaluating the effects of amiodarone or verapamil on atorvastatin have not been conducted. Both amiodarone and verapamil are known to inhibit CYP3A4 activity and co-administration

with atorvastatin may result in increased exposure to atorvastatin. Therefore, a lower maximum dose of atorvastatin should be considered and appropriate clinical monitoring of the patient is recommended when concomitantly used with moderate CYP3A4 inhibitors. Appropriate clinical monitoring is recommended after initiation or following dose adjustments of the inhibitor.

Cytochrome P450 3A4 inducers:

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

Transport protein inhibitors

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

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

Ezetimibe

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

Colestipol:
Plasma concentrations of atorvastatin and its active metabolites were lower (by approximately 25%) when colestipol was co-administered with atorvastatin. However, lipid effects were greater when atorvastatin and colestipol were co-administered than when either medicinal product was given alone.

Fusidic acid
Interaction studies with atorvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with atorvastatin and fusidic acid given concurrently. The mechanism of this

interaction is not known. Patients should be closely monitored and temporary suspension of atorvastatin treatment may be appropriate.

Effect of atorvastatin on co-administered medicinal products

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

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

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

Table 1: Effect of co-administered medicinal products on the pharmacokinetic of atorvastatin

Co-administered medicinal product and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Clinical Recommendation[#]
Tipranavir 500 mg BID/ Ritonavir 200 mg BID, 8 days (days 14 to 21)	40 mg on day 1, 10 mg on day 20	↑9.4 fold	In cases where co-administration with atorvastatin is necessary, do not exceed 10 mg atorvastatin daily. Clinical monitoring of these patients is recommended
Ciclosporin 5.2 mg/kg/day, stable dose	10 mg OD for 28 days	↑8.7 fold	

Lopinavir 400 mg BID/ Ritonavir 100 mg BID, 14 days	20 mg OD for 4 days	↑5.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.
Clarithromycin 500 mg BID, 9 days	80 mg OD for 8 days	↑4.4 fold	
Saquinavir 400 mg BID/ Ritonavir (300 mg BID from days 5-7, increased to 400 mg BID on day 8), days 5-18, 30 min after atorvastatin dosing	40 mg OD for 4 days	↑3.9 fold	In cases where co-administration with atorvastatin is necessary, lower maintenance doses of atorvastatin are recommended. At atorvastatin doses exceeding 40 mg, clinical monitoring of these patients is recommended.
Darunavir 300 mg BID/ Ritonavir 100 mg BID, 9 days	10 mg OD for 4 days	↑3.3 fold	
Itraconazole 200 mg OD, 4 days	40 mg SD	↑3.3 fold	
Fosamprenavir 700 mg BID/ Ritonavir 100 mg BID, 14 days	10 mg OD for 4 days	↑2.5 fold	
Fosamprenavir 1400 mg BID, 14 days	10 mg OD for 4 days	↑2.3 fold	
Nelfinavir 1250 mg BID, 14 days	10 mg OD for 28 days	↑1.7 fold^	No specific recommendation
Grapefruit Juice, 240 mL OD *	40 mg, SD	↑37%	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended.
Diltiazem 240 mg OD, 28 days	40 mg, SD	↑51%	After initiation or following dose adjustments of diltiazem, appropriate clinical monitoring of these patients is recommended.
Erythromycin 500 mg QID, 7 days	10 mg, SD	↑33%^	Lower maximum dose and clinical monitoring of these patients is recommended.
Amlodipine 10 mg, single	80 mg, SD	↑18%	No specific

dose			recommendation.
Cimetidine 300 mg QID, 2 weeks	10 mg OD for 4 weeks	□↓less than 1%^	No specific recommendation.
Antacid suspension of magnesium and aluminium hydroxides, 30 mL QID, 2 weeks	10 mg OD for 4 weeks	↓35%^	No specific recommendation.
Efavirenz 600 mg OD, 14 days	10 mg for 3 days	↓41%	No specific recommendation.
Rifampin 600 mg OD, 7 days (co-administered)	40 mg SD	↑30%	If co-administration cannot be avoided, simultaneous co-administration of atorvastatin with rifampin is recommended, with clinical monitoring.
Rifampin 600 mg OD, 5 days (doses separated)	40 mg SD	↓80%	
Gemfibrozil 600 mg BID, 7 days	40mg SD	↑35%	Lower starting dose and clinical monitoring of these patients is recommended.
Fenofibrate 160 mg OD, 7 days	40mg SD	↑3%	Lower starting dose and clinical monitoring of these patients is recommended.

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

[#] See sections 4.4 and 4.5 for clinical significance.

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

[^] Total atorvastatin equivalent activity

Increase is indicated as "↑", decrease as "↓"

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

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

Atorvastatin and dosing regimen	Co-administered medicinal product		
	Medicinal product/Dose (mg)	Change in AUC[&]	Clinical Recommendation
80 mg OD for 10 days	Digoxin 0.25 mg OD, 20 days	↑15%	Patients taking digoxin should be monitored appropriately.
40 mg OD for 22 days	Oral contraceptive OD, 2 months - norethindrone 1 mg -ethinyl estradiol	↑28% ↑19%	No specific recommendation.

	35 µg		
80 mg OD for 15 days	* Phenazone, 600 mg SD	↑3%	No specific recommendation

[&] Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change)
[*] Co-administration of multiple doses of atorvastatin and phenazone showed little or no detectable effect in the clearance of phenazone.

Increase is indicated as "↑", decrease as "↓"
OD = once daily; SD = single dose

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Infections and infestations:
Common: nasopharyngitis

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

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

Blood and lymphatic disorders:
Rare: thrombocytopaenia.

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

Endocrine disorders:
Common: hyperglycaiemia
Uncommon: hypoglycaemia, weight gain, anorexia.

Psychiatric disorders:
Uncommon: nightmare, insomnia.

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

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

Hepatobiliary disorders:
Uncommon: hepatitis.
Rare: cholestasis.

Very rare: hepatic failure.

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

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

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

Reproductive system and breast disorders:
Very rare: gynaecomastia.

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

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

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

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

The following adverse events have been reported with some statins:

- Sexual dysfunction.
- Depression.
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

4.9 Overdose

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

atorvastatin binding to plasma proteins, haemodialysis is not expected to significantly enhance atorvastatin clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, HMG-CoA reductase inhibitors, ATC code: C10A A05.

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

Atorvastatin lowers plasma cholesterol and lipoproteins serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of LDL hepatic 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-cholesterol in patients with homozygous familial hypercholesteroaemia, a population which does not normally respond well to lipid lowering medication.

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

Reductions in total cholesterol, LDL-cholesterol and apolipoprotein B have been proven to reduce the risk of cardiovascular events and cardiovascular mortality.

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

Atherosclerosis

In the Reversing Atherosclerosis with Aggressive Lipid-Lowering study (REVERSAL) the effect of intensive lipid lowering with atorvastatin 80 mg and standard degree of lipid lowering with pravastatin 40 mg on coronary atherosclerosis was assessed by intravascular ultrasound (IVUS), during angiography, in patients with coronary heart disease. In this randomised, double-blind, multicenter controlled clinical trial, IVUS was performed at baseline and at 18

months in 502 patients. In the atorvastatin group (n=253) there was no progression of the atherosclerosis.

The median per cent 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 cholesterol 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 cholesterol was reduced to a mean of 2.85 mmol/l ± 0.7 (110 mg/dl ± 26) from a baseline 3.89 mmol/l ± 0.7 (150 mg/dl ± 26) ($p<0.0001$). Atorvastatin also significantly reduced mean total cholesterol by 34.1% (pravastatin: -18.4%, $p<0.0001$), mean triglyceride levels by 20% (pravastatin: -6.8%, $p<0.0009$) and average apolipoprotein B by 39.1% (pravastatin: -22.0%, $p<0.0001$). Atorvastatin increased mean HDL cholesterol by 2.9% (pravastatin: +5.6%, p=NS). There was an average reduction of 36.4% in CRP in the atorvastatin group, compared to 5.2% in the pravastatin group ($p<0.0001$).

The results of this study were obtained with the 80 mg dose strength, and cannot be extrapolated to lower dose strengths.

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

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

Acute coronary syndrome

The MIRACL study evaluated the effect of 80 mg atorvastatin on 3086 patients (atorvastatin n=1,538; placebo n=1,548) with an acute coronary syndrome (non-Q-wave myocardial infarction 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, non-fatal myocardial infarction, resuscitated cardiac arrest or angina pectoris with evidence of myocardial ischaemia requiring hospitalisation, indicating a risk reduction of 16% (p=0.048). This was 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 randomised, double-blind, placebo-controlled study the Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm, (ASCOT-LLA). Patients were hypertensive, aged 40-79, with no

previous myocardial infarction or treatment for angina, and with total cholesterol levels ≤ 6.5 mmol/l (251 mg/dl). All patients presented had at least three of the following predefined cardiovascular risk factors: male gender, age ≥ 55, smokers, diabetes, history of coronary heart disease (CHD) in a first-degree relative, TC:HDL-C > 6, peripheral vascular disease, left ventricular hypertrophy, prior cerebrovascular event, specific abnormality in the ECG, proteinuria/albuminuria. Not all patients included 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 revascularisation procedures	20%	389 vs. 483	1,9%	0,0008
Total coronary events	29%	178 vs 247	1,4%	0,0006

[1]Based on the 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 patients 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, CARDS (the Collaborative Atorvastatin Diabetes Study) in patients with type 2 diabetes, aged 40-75, without prior history of cardiovascular disease and with LDL cholesterol ≤ 4.14 mmol/L (160 mg/dl) and TG ≤ 6.78 mmol/L (600 mg/dl). All patients had at least one of the following risk factors: hypertension, current smoking, retinopathy, microalbuminuria or macroalbuminuria.

Patients were treated with 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, 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
Stroke (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 period 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 difference in the treatment effect by patient's gender, age or baseline LDL cholesterol levels. A favourable trend was observed with regard to the mortality rate (82 deaths in the placebo group vs. 61 deaths in the atorvastatin group, p=0.0592).

Recurrent stroke

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

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

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

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

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

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

5.2 Pharmacokinetic properties

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

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

Biotransformation: Atorvastatin is metabolised by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolized via glucuronidation. In vitro, inhibition of HMG-CoA reductase by the ortho- and parahydroxylates 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 extra-hepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20-30 hours due to the contribution of active metabolites.

Special populations

Elderly: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly patients than in young adults, while the effects on lipids were comparable to those observed in younger populations.

Paediatric: No pharmacokinetic data is available for paediatric population.

Gender: Concentrations of atorvastatin and its active metabolites in women differ from those in men (Women: C_{max} is approximately 20% higher and AUC 10% lower). These differences between women and men were not clinically significant, and did not lead to clinically significant differences in lipid effects.

Renal insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approx. 16-fold in C_{max} and approx. 11-fold in AUC) in patients with chronic alcoholic liver disease (Child-Pugh B).

SLOC1B1 polymorphism: Hepatic uptake of all HMG-CoA reductase inhibitors including atorvastatin, involves the OATP1B1 transporter. In patients with SLCO1B1 polymorphism there is a risk of increased exposure of atorvastatin, which may lead to an increased risk of rhabdomyolysis (see section 4.4). Polymorphism in the gene encoding OATP1B1 (SLCO1B1 c.521CC) is associated with a 2.4-fold higher atorvastatin exposure (AUC) than in individuals without this genotype variant (c.521TT). A genetically impaired hepatic uptake of atorvastatin is also possible in these patients. Possible consequences for the efficacy are unknown.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Monohydrate lactose, magnesium stearate, sodium laurylsulphate, microcrystalline cellulose (E-460), anhydrous colloidal silica, butyl hydroxyanisol (E-320), crospovidone, sodium bicarbonate, sucrose, sodium tristereate, macrogol stearate 40, dimethicone, 2, Bromo-2-nitropropane-1,3-diol.

Coating: monohydrate lactose, hypromellose (E-464), titanium dioxide (E-171), macrogol 4000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original container.

6.5 Nature and contents of container

The tablets are packaged in Aluminium/Aluminium blisters in packages of 28 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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31620 Huarte-Pamplona (Navarre)

8. MARKETING AUTHORISATION NUMBER(S)

Pending