LIPITOR®

Atorvastatin

1. Trade Name of The Medicinal Product
Lipitor®

2. Qualitative and Quantitative Composition
1 film coated tablet contains 10.85 mg atorvastatin-calcium (2:1). $3H_2O$ corresponding to 10 mg atorvastatin
1 film coated tablet contains 21.69 mg atorvastatin-calcium (2:1). $3H_2O$ corresponding to 20 mg atorvastatin
1 film coated tablet contains 43.38 mg atorvastatin-calcium (2:1). $3H_2O$ corresponding to 40 mg atorvastatin

3. Pharmaceutical Form
Film coated tablets

4. Clinical Particulars
4.1. Therapeutic Indications
Lipitor® is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolemia including familial hypercholesterolemia (heterozygous variant) or combined (mixed) hyperlipidemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other nonpharmacological measures is inadequate.
Lipitor® is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g.LDL apheresis) or if such treatments are unavailable.
4.2. Dosage and Administration
The patient should be placed on a standard cholesterol-lowering diet before receiving Lipitor® and should continue on this diet during treatment with Lipitor®.
The usual starting dose is 10 mg once a day. Doses should be individualized according to baseline LDL-C levels, the goal of therapy, and patient response. Adjustment of dosage should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day. Doses may be given at any time of day with or without food.
Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia
The majority of patients are controlled with 10 mg Lipitor® once a day. A therapeutic response is evident within 2 weeks, and the maximum response is usually achieved within 4 weeks. The response is maintained during chronic therapy.
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.
Heterozygous Familial Hypercholesterolemia
Patients should be started with Lipitor® 10 mg daily. Doses should be individualized 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 Lipitor®.
Homozygous Familial Hypercholesterolemia
In a companionate-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%. Lipitor® was administered at doses up to 80 mg/day.
The dosage of Lipitor® in patients with homozygous familial hypercholesterolemia is 10 to 80 daily. Lipitor® should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.
Dosage in Patients With Renal Insufficiency
Renal disease has no influence on the plasma concentrations nor lipid effects of Lipitor®; thus, no adjustment of dose is required.
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. 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
Lipitor® is contraindicated in patients with hypersensitivity to any component of this medication, active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal, myopathy, during pregnancy, while breast-feeding, and in women of child-bearing potential not using appropriate contraceptive measures.
4.4. Special Warnings and Special 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 Lipitor® is recommended.
Lipitor® should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.
Skeletal Muscle Effects
Uncomplicated myalgia, including muscle cramps, has been reported in Lipitor®-treated patients. Lipitor® therapy should be discontinued if markedly elevated creatine phosphokinase (CPK) levels occur or myopathy is diagnosed or suspected. Patients who develop any signs or symptoms suggestive of myopathy should have CPK levels measured. Should significant increases in CPK (greater than ten times the upper limit of normal) persist, reduction of dose or withdrawal of Lipitor® is recommended.
(see 4.5 Interaction With Other Medicaments and Other Forms of Interaction)
4.5. Interaction With Other Medicaments and Other Forms of Interaction
The risk of myopathy during treatment with other drugs in this class is increased with concurrent administration of cyclosporin, 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.
Atorvastatin is metabolized by cytochrome P450 3A4.
Based on experience with other HMG-CoA reductase inhibitors, caution should be exercised when Lipitor® is administered with inhibitors of cytochrome P450 3A4 (e.g. cyclosporins, macrolide antibiotics including erythromycin and clarithromycin, and azole antifungals including itraconazole). The effect of inducers of cytochrome P450
3A4 (e.g. rifampicin or phenytoin) on Lipitor® is unknown. The possible interaction with other substrates of this isozyme is unknown but should be considered for other drugs with a narrow therapeutic index, for example, antiarrhythmic agents Class III including amiodarone.
In clinical studies in which Lipitor® was administered with antihypertensives or hypoglycemic agents, no clinically significant interactions were seen.
Amlodipine: Atorvastatin pharmacokinetics were not altered by the co-administration of atorvastatin 80 mg and amlodipine 10mg at steady state.
Erythromycin, Clarithromycin: Co-administration of atorvastatin 10 mg OD and erythromycin (500mg 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.
(See also Section 4.4. Special Warnings and Special Precautions for Use: Skeletal Muscle Effects).
Digoxin: When multiple doses of digoxin and 10 mg atorvastatin were co-administered, steady-state plasma digoxin concentrations were unaffected. However, digoxin concentrations increased approximately 20% following administration of digoxin with 80 mg atorvastatin daily. Patients taking digoxin should be monitored appropriately.
Oral contraceptives: Co-administration of Lipitor® with an oral contraceptive produced increases in concentrations of norethindrone and ethinyl estradiol. These increased concentrations should be considered when selecting oral contraceptive doses.
Colestipol: Plasma concentrations of atorvastatin and its active metabolites were lower (approximately 25%) when colestipol was coadministered with Lipitor®. However, lipid effects were greater when Lipitor® and colestipol were co-administered than when either drug was given alone.
Antacid: Co-administration of Lipitor® with an oral antacid suspension containing magnesium and aluminium hydroxides decreased plasma concentrations of atorvastatin and its active metabolites approximately 35%; however, LDL-C reduction was not altered.
Warfarin: Co-administration of Lipitor® and warfarin caused a small decrease in prothrombin time during the first days of dosing which returned to normal within 15 days of Lipitor® treatment. Nevertheless, patients receiving warfarin should be closely monitored when Lipitor® is added to their therapy.

Phenazone: Co-administration of multiple doses of Lipitor® and phenazone showed little or no detectable effect in the clearance of phenazone.
Cimetidine: An interaction study with cimetidine and Lipitor® was conducted, and no interaction was seen.

4.6. Pregnancy and Lactation
Lipitor® is contraindicated in pregnancy and while breast feeding. Women of childbearing 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 fetuses. 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 drug or its metabolites are excreted in human milk.

4.7. Effects on Ability to Drive and use Machines
There is no pattern of reported adverse events suggesting that patients taking Lipitor® will have any impairment of ability to drive and use hazardous machinery.

4.8. Adverse Effects
Lipitor® is generally well-tolerated. Adverse reactions have usually been mild and transient. Less than 2% of patients were discontinued from clinical trials due to side effects attributed to Lipitor®.
The most frequent (1% or more) adverse effects associated with Lipitor® therapy in patients participating in controlled clinical studies are constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhea, and insomnia.
As with other HMG-CoA reductase inhibitors, elevated serum transaminases have been reported in patients receiving Lipitor®. 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 Lipitor®. 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 Lipitor®, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% Lipitor®-treated patients. Of these patients, 0.1% had concurrent muscle pain, tenderness, or weakness.
The following rare adverse effects have been reported. Not all effects listed have necessarily been associated with Lipitor® therapy: myositis, myopathy, rhabdomyolysis, paresthesia, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomiting, alopecia, pruritus, rash, arthralgia, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), impotence, hyperglycemia, hypoglycemia, chest pain, dizziness, thrombocytopenia and allergic reactions including angioneurotic edema.

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

5. Pharmacological Properties

5.1. Pharmacodynamics
Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the high affinity LDL receptor.
Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.
Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in patients with homozygous familial hypercholesterolemia, a population that has not usually responded to lipid-lowering medications.
Atorvastatin has been shown to reduce 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 A-I in a dose response study. These results are consistent in patients with heterozygous familial hypercholesterolemia, nonfamilial forms of hypercholesterolemia, and mixed hyperlipidemia, including patients with non insulin-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.

5.2. Pharmacokinetic Properties
Pharmacokinetics and drug metabolism
Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is ≥98% bound to plasma proteins.
Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. *In vitro*, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.
Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20-30 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.
Pediatric: Pharmacokinetic data in the pediatric population are not available.
Gender: Concentrations of atorvastatin and its active metabolites in women differ (approximately 20% higher for C_{max} and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.
Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.
Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in C_{max} and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

5.3. Preclinical safety data
Atorvastatin was not carcinogenic in rats. The maximum dose used was 63-fold higher than the highest human dose (80 mg/day) on a mg/kg body-weight basis and 8- to 16-fold higher based on AUC (0-24) values as determined by total inhibitory activity. In a 2-year study in mice, incidences of hepatocellular adenoma in males and hepatocellular carcinomas in females were increased at the maximum dose used, and the maximum dose used was 250-fold higher than the highest human dose on a mg/kg body-weight basis. Systemic exposure was 6- to 11-fold higher based on AUC (0-24). Atorvastatin did not demonstrate mutagenic or clastogenic potential in 4 *in vitro* tests with and without metabolic activation and in 1 *in vivo* assay. 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
The film coated tablets contain the following excipients:
Calcium carbonate - Microcrystalline cellulose - Lactose monohydrate - Croscarmellose sodium - Polysorbate 80 - Hydroxypropyl cellulose - Magnesium stearate - Opadry white YS-1-7040 (Hydroxypropyl methylcellulose - Polyethylene glycol - Titanium dioxide-Talc) Simethicone emulsion, USP (Dimeticone - Silicium dioxide) - Candelilla wax

6.2. Incompatibilities: None

6.3. Special precautions for storage: None

6.4. Nature and contents of container
Lipitor® 10 mg, 20 mg and 40 mg are supplied in blister packs of 30 tablets.

6.5 Instructions for use/handling
No special instructions needed

7. Date of Last Revision of The Text: July 2001

Manufactured by Godecke, Parke-Davis Germany