**UNDESIRABLE EFFECTS**

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

After intravenous administration to adult patients, 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 interaction between atorvastatin and gemfibrozil/fibric acid derivatives could lead to increased plasma concentrations of atorvastatin. Therefore, the benefit and the risk of concurrent treatment should be carefully weighed (see Special warnings and special precautions for use).

**THERAPEUTIC INDICATIONS**

Atorvastatin is contraindicated in pregnancy and while breast feeding. Women of child-bearing potential should use appropriate contraceptive measures. The safety of Atorvastatin in pregnant women is not established. Breast-fed infants should be observed for any adverse effects (see Concomitant therapy).

**CLINICAL PARTICULARS**

**Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia**

The majority of patients are controlled with Atorvastatin 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually reached within 12 weeks of treatment.

**Heterozygous familial hypercholesterolaemia**

If CPK levels are significantly elevated (> 5 times ULN) at baseline, treatment should not be started.

**Dosage**

- 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 recommended.

- For patients with a previous history of elevated CPK levels but no history of myopathy or myalgia, it may be necessary to discontinue atorvastatin and to consider the use of an alternative HMG-CoA reductase inhibitor at a lower dose.

**Erythromycin, clarithromycin**

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.

**Risk of rhabdomyolysis**

Risk of rhabdomyolysis is increased when atorvastatin is administered concomitantly with certain medicaments such as: ciclosporin, erythromycin, clarithromycin, macrolide antibiotics, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors. Concomitant administration of atorvastatin and these medicaments should be avoided. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivates, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors. Concomitant administration of atorvastatin and these medicaments should be avoided. The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with concurrent administration of ciclosporin, fibric acid derivates, macrolide antibiotics including erythromycin and clarithromycin, nefazodone, azole antifungals including itraconazole and HIV protease inhibitors. Concomitant administration of atorvastatin and these medicaments should be avoided.
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.

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 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, showing that atorvastatin was more effective than pravastatin in reducing atheroma volume. There was no progression of atherosclerosis.

Patients were treated with atorvastatin or placebo for a median of 5 years, during which the mean total cholesterol level in the atorvastatin group was 4.7 mmol/l (181mg/dl) versus 7.5 mmol/l (288mg/dl) in the placebo group (p < 0.0001).

The reduction in total cholesterol, LDL cholesterol and apolipoprotein B provided demonstrable evidence of a reduction in the risk of cardiovascular events and a benefit in patients 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%).

Atorvastatin is a cholesterol-lowering medicinal product that is effective in reducing LDL cholesterol by 40-50% and total cholesterol by 25-30%.

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 (HMG-CoA) to mevalonic acid and cholesterol.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin is not expected to significantly enhance atorvastatin clearance.

The ASCOT-LLA study (Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm), a randomised, double-blind, placebo-controlled study, the effect of atorvastatin on fatal coronary heart disease and non-fatal myocardial infarction was assessed in patients treated with amlodipine (n = 5,000) and either atorvastatin 10 mg daily (n = 5,168) or placebo (n = 5,137). The primary endpoint of the study was a composite endpoint of fatal coronary heart disease and non-fatal myocardial infarction (CHD death, unstable angina, CABG, PTCA, revascularization, stroke)...

The primary endpoint (fatal coronary heart disease and non-fatal myocardial infarction) was significantly reduced by atorvastatin in patients treated with amlodipine (HR 0.79; 95% CI 0.65-0.97; p = 0.027). There was a significant reduction in the incidence of cardiovascular disease events in the atorvastatin group compared with the placebo group (p = 0.027). The reduction in total coronary events was 22%...