Atorvastatin

Action
Reduction of elevated cholesterol and triglyceride values by inhibiting the enzyme HMG-CoA reductase which is the rate limiting step in the cholesterol biosynthesis in the liver.

Indications
Vastor is indicated as an adjuvant 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.

Vastor is also indicated to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjuvant to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Dosage and Administration
The patient should be placed on a standard cholesterol-lowering diet before receiving Vastor and should continue on this diet during treatment with Vastor.

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 anytime of day with or without food.

Primary Hypercholesterolemia and Combined (Mixed) Hyperlipidemia
The majority of patients are controlled with 10 mg Vastor 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).

Heterozygous Familial Hypercholesterolemia
Patients should be started with Vastor 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 Vastor.

Homozygous Familial Hypercholesterolemia
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%. Vastor was administered at doses up to 80 mg/day.

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

Patients With Renal Insufficiency
Renal disease has no influence on the plasma concentrations nor lipid effects of Vastor; 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
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 postnatal 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.

Effects on ability to drive and use machines
There is no pattern of reported adverse events suggesting that patients taking Atorvastatin will have any impairment of ability to drive and use hazardous machinery.

Drug Interactions
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 Atorvastatin 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 Atorvastatin 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 Atorvastatin was administered with antihypertensives or hypoglycemic agents, no clinically significant interactions were seen.

Pregnancy and Lactation
Atorvastatin 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 postnatal 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.

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

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

Side Effects
Atorvastatin 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 Atorvastatin.

The most frequent (1% or more) adverse effects associated with Atorvastatin 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 Atorvastatin. 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% of patients on Atorvastatin. 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 Atorvastatin, similar to other HMG-CoA reductase inhibitors in clinical trials. Levels above 10 times the normal upper range occurred in 0.4% of Atorvastatin 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 Atorvastatin 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.
**Storage Conditions**
Store in a dry place below 25°C.

**Overdosage**
Specific treatment is not available for Atorvastatin 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.

**Presentations**
Tablets:
VASTOR 10 mg: Atorvastatin 10 mg
VASTOR 20 mg: Atorvastatin 20 mg
VASTOR 40 mg: Atorvastatin 40 mg
VASTOR 80 mg: Atorvastatin 80 mg
Excipients: CaCO₃, Microcrystalline cellulose, Lactose, Cross carmellose sodium, hydroxypropyl cellulose, Tween 80, Magnesium stearate, Opadry white (YS-1-7040).