TORVACOL®

DESCRIPTION

TORVACOL is the trade name of Atorvastatin, an HMG-CoA reductase inhibitor antihyperlipidemic.
Each **TORVACOL 10, 20,** and **40** Tablet contains Atorvastatin 10, 20 and 40 mg, respectively, as Atorvastatin Calcium.

CHEMISTRY

Atorvastatin calcium is: [R-(R*,R*)]-2-(4-Fluorphenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

CLINICAL PHARMACOLOGY

TORVACOL (Atorvastatin) competitively inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme that catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol biosynthesis in the liver. Atorvastatin also increases the number of hepatic LDL receptors on the cell surface to enhance uptake and catabolism of LDL. Moreover, Atorvastatin decreases LDL production and the number of LDL particles. Consequently, it reduces total-cholesterol (total-C), LDL-C, and apolipoprotein (apo) B, which promote human atherosclerosis and are risk factors for developing cardiovascular disease. It also reduces LDL precursor, VLDL-C, and triglyceride levels; and produces an increase in HDL-C associated with decreased cardiovascular risk.
Atorvastatin is rapidly absorbed, the extent of absorption increasing in proportion to the dose. Atorvastatin has a low systemic availability due to pre-systemic clearance (absolute bioavailability ~12%). The rate and extent of absorption are decreased when given with food, but LDL-C reduction is the same. Atorvastatin has very high protein binding (98%), and is extensively metabolized to active metabolites by cytochrome P450 3A4. It is primarily eliminated by the fecal route (biliary).

INDICATIONS

- ❑ Adjunct to diet to reduce elevated total-C, LDL-C, apo B, and triglyceride levels in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb).
- ❑ Adjunct to diet in treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV).
- ❑ Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet (Fredrickson Type III).
- ❑ Adjunct to other lipid-lowering treatments in patients with homozygous familial hypercholesterolemia in order to reduce total-C and LDL-C.
- ❑ As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  - LDL-C remains ≥ 190mg/dL; or,
  - LDL-C remains ≥ 160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors are present in the pediatric patient.

DOSAGE

Usual adult dose

- ❑ Primary hypercholesterolemia and mixed dyslipidemia: The recommended starting dose is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range is 10 to 80 mg once daily.
- ❑ Homozygous familial hypercholesterolemia: 10 to 80 mg a day.

Usual pediatric dose

- ❑ Heterozygous familial hypercholesterolemia in patients 10 to 17 years of age: The recommended starting dose is 10 mg/day; the maximum recommended dose is 20 mg/day.
- ❑ Eight pediatric patients (not less than 9 years of age) with homozygous familial hypercholesterolemia (FH) were treated with Atorvastatin at doses of up to 80 mg per day for 1 year with no clinical or biochemical abnormalities reported.

Notes

- ❑ After initiating or changing **TORVACOL** dose, lipid concentrations (LDL-C recommended) should be measured within 2 to 4 weeks, and dose adjusted as needed.
- ❑ **TORVACOL** can be given as a single dose at any time of the day, with or without food. The maximum daily dose is 80 mg.
- ❑ **TORVACOL** may be used with colestipol or cholestyramine for additive antihyperlipidemic effects.
- ❑ **TORVACOL** has not been studied in controlled clinical trials involving patients younger than 10 years of age.

ADVERSE EFFECTS

- ❑ Less frequent effects: abdominal pain; constipation; diarrhea; dyspepsia (heartburn, indigestion, stomach discomfort); flatulence (belching, excessive gas); skin rash.
- ❑ Rare incidence: muscle disorders, such as leg cramps; uncomplicated myalgia (muscle pain); myopathy and/or rhabdomyolysis (fever; muscle cramp, pain, stiffness, or weakness; unusual tiredness; serum creatine kinase (CK) > 10 times the upper limit of normal); and myositis.

USE IN PREGNANCY

The safety of Atorvastatin in pregnant women has not been established. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy. Atorvastatin should be administered to women of childbearing age only if contraception is guaranteed. FDA Pregnancy Category X.

USE IN LACTATION

Atorvastatin is distributed into the milk of lactating rats. It is not known whether it is distributed into breast milk. HMG-CoA reductase inhibitors are contraindicated in women who are breast-feeding because inhibition of cholesterol synthesis may cause serious adverse effects in the nursing infant.

INTERFERENCE WITH CLINICAL AND LABORATORY TESTS

- Atorvastatin may increase serum transaminase levels. Therefore, it is recommended that hepatic function be determined prior to initiation of treatment and at 6 and 12 weeks of treatment or at a dosage increase, and periodically thereafter (semiannually).
- Atorvastatin may increase serum creatine kinase (CK) levels. Periodic serum CK determinations are recommended in patients developing muscle pain, tenderness, or weakness during therapy or in patients receiving azole antifungals, erythromycin, gemfibrozil, cyclosporine, or niacin with Atorvastatin. Atorvastatin should be discontinued if marked elevations occur.

DRUG INTERACTIONS

- The use of Atorvastatin with azole antifungals, erythromycin, fibric acid derivatives, cyclosporine, or niacin (nicotinic acid) can increase risk of myopathy.
- The co-administration of Atorvastatin with digoxin lead to an increase in steady-state plasma digoxin concentrations by 20%. Digoxin levels should be monitored.
- The concomitant administration of Atorvastatin with an oral contraceptive led to an increase in AUC values for norethindrone and ethinyl estradiol by 30% and 20%, respectively. In choosing an oral contraceptive, these increases should be considered.
- Elevations in transaminase values may occur in case of substantial use of Alcohol.
- Grapefruit juice in large amounts, has been shown to interfere with the metabolism of Atorvastatin, causing increases in C_{max} and AUC. It is recommended that Atorvastatin not be administered with large amounts of grapefruit juice.

CONTRAINDICATIONS

- Hypersensitivity to Atorvastatin.
- Active hepatic disease including chronic alcoholic liver disease, Childs-Pugh Index grade A or B disease, and unexplained, persistent elevation of transaminase values (Atorvastatin may potentially accumulate).
- Pregnancy and lactation.

WARNINGS

Risk-benefit should be considered when the following medical problems exist:

- Severe electrolyte, endocrine, or metabolic disorders; hypotension; severe, acute infection; uncontrolled seizures; major surgery or trauma: these conditions may predispose a patient to the development of renal failure, secondary to rhabdomyolysis. Atorvastatin should be discontinued or temporarily withheld.
- Patients with a history of hepatic disease: elevations in transaminase values may occur.

OVERDOSE

No specific treatment exists for Atorvastatin overdose. Treatment of overdose should be symptomatic and supportive. Atorvastatin is not expected to be removed significantly by hemodialysis because of its extensive binding to plasma proteins.

PRECAUTIONS

- Dosage modification in patients with renal impairment is not necessary because Atorvastatin does not undergo substantial renal excretion.
- Atorvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. Patients who develop any signs or symptoms suggestive of myopathy should have CK levels measured. Should significant increases in CK persist, reduction of dose or withdrawal of atorvastatin is recommended.

HOW SUPPLIED

- Boxes of 30 blistered tablets of **TORVACOL 10** Tablets.
- Boxes of 30 blistered tablets of **TORVACOL 20** Tablets.
- Boxes of 30 blistered tablets of **TORVACOL 40** Tablets.
- Boxes of 14 blistered tablets of **TORVACOL 40** Tablets.
- Hospital packs of different presentations.

Store according to conditions specified on the package.
Do not use after the expiry date shown on the package.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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Prescribing Information Available Upon Request

JPM

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