Cougar Tablets*

کوگر ٹیبلٹس

COMPOSITION: *Each tablet contains:* Rosuvastatin (Calcium)* 5, 10 & 20 mg, respectively.

DESCRIPTION: COUGAR (Rosuvastatin Calcium) is a synthetic lipid-lowering agent. Rosuvastatin calcium is bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2Ca$. Its molecular weight is 1001.14.

PHARMACOLOGY: Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Rosuvastatin produces its lipid-modifying effects in two ways. First, it increases the number of hepatic LDL receptors on the cell-surface to enhance uptake and catabolism of LDL. Second, rosuvastatin inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles. In the bloodstream, cholesterol and triglycerides (TG) circulate as part of lipoprotein complexes. With ultracentrifugation, these complexes separate into very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) fractions that contain apolipoprotein B-100 (ApoB-100) and high-density lipoprotein (HDL) fractions. Cholesterol and TG synthesized in the liver are incorporated into VLDL and secreted into the circulation for delivery to peripheral tissues. TG are removed by the action of lipases and in a series of steps, the modified VLDL is transformed first into IDL and then into cholesterol-rich LDL. IDL and LDL are removed from the circulation mainly by high affinity ApoB/E receptors, which are expressed to the greatest extent on liver cells. HDL is hypothesized to participate in the reverse transport of cholesterol from tissues back to the liver. In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%. Administration of rosuvastatin with food does not affect the AUC. Plasma concentrations of rosuvastatin do not differ following evening or morning drug administration. Significant LDL-C reductions are seen when rosuvastatin is given with or without food and regardless of the time of day of drug administration. Mean volume of distribution at steady-state of rosuvastatin is approximately 134 liters. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations. Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9 and *in vitro* studies have demonstrated that N-desmethyl rosuvastatin has approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Overall, greater than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin. Following oral administration, rosuvastatin and its metabolites are primarily excreted in the feces (90%). The elimination half-life (t1/2) of rosuvastatin is approximately 19 hours.

INDICATIONS: Hyperlipidemia & Mixed Dyslipidemia: As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb). **Hypertriglyceridemia:** As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IV). **Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia):** As an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia. **Homozygous Familial Hypercholesterolemia:** To reduce LDL-C, total-C and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **Slowing of the Progression of Atherosclerosis:** As adjunctive therapy to diet to slow the progression of Atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C to target levels.

CONTRAINDICATIONS: Rosuvastatin is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases. HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.

POSSIBLE ADVERSE EFFECTS: Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. The most frequent adverse events thought to be related to rosuvastatin are myalgia, constipation, asthenia, abdominal pain and nausea.

DRUG INTERACTIONS: *Cytochrome P450 3A4: In vitro* and *in vivo* data indicate that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. *Ketoconazole:* Coadministration of ketoconazole (200 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in no change in plasma concentrations of rosuvastatin. *Erythromycin:* Coadministration of erythromycin (500 mg four times daily for 7 days) with rosuvastatin (80 mg) decreased AUC and C_{max} of rosuvastatin by 20% and 31%, respectively. *Itraconazole:* Itraconazole (200 mg once daily for 5 days) resulted in a 39% and 28%

increase in AUC of rosuvastatin after 10 mg and 80 mg dosing, respectively. *Fluconazole:* Coadministration of fluconazole (200 mg once daily for 11 days) with rosuvastatin (80 mg) resulted in a 14% increase in AUC of rosuvastatin. *Cyclosporine:* Coadministration of cyclosporine with rosuvastatin resulted in no significant changes in cyclosporine plasma concentrations. However, C_{max} and AUC of rosuvastatin increased 11- and 7-fold, respectively. *Warfarin:* Coadministration of warfarin (25 mg) with rosuvastatin (40 mg) did not change warfarin plasma concentrations but increased the International Normalized Ratio (INR). *Digoxin:* Coadministration of digoxin (0.5 mg) with rosuvastatin (40 mg) resulted in no change to digoxin plasma concentrations. *Fenofibrate:* Coadministration of fenofibrate (67 mg three times daily) with rosuvastatin (10 mg) resulted in no significant changes in plasma concentrations of rosuvastatin or fenofibrate. *Gemfibrozil:* Coadministration of gemfibrozil (600 mg twice daily for 7 days) with rosuvastatin (80 mg) resulted in a 90% and 120% increase for AUC and C_{max} of rosuvastatin, respectively. *Antacid:* Coadministration of an antacid (aluminum and magnesium hydroxide combination) with rosuvastatin (40 mg) resulted in a decrease in plasma concentrations of rosuvastatin by 54%. However, when the antacid was given 2 hours after rosuvastatin, there were no clinically significant changes in plasma concentrations of rosuvastatin. *Oral Contraceptives:* Coadministration of oral contraceptives (ethinyl estradiol and norgestrel) with rosuvastatin resulted in an increase in plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively.

WARNINGS: *Liver Enzymes:* HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. It is recommended that liver function tests should be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose and periodically (e.g., semiannually) thereafter. *Myopathy/Rhabdomyolysis:* Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class. *Pediatric Use:* The safety and effectiveness in pediatric patients have not been established. *Geriatric Use:* The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age.

DOSAGE & ADMINISTRATION: The dose range for COUGAR is 5 to 40 mg orally once daily. The patient should be placed on a standard cholesterol-lowering diet before receiving COUGAR and should continue on this diet during treatment. COUGAR can be administered as a single dose at any time of day, with or without food. *Hyperlipidemia, Mixed Dyslipidemia, Hypertriglyceridemia, Primary Dysbetalipoproteinemia (Type III Hyperlipoproteinemia) & Slowing of the Progression of Atherosclerosis:* The recommended starting dose of COUGAR is 10 mg once daily. For patients with marked hyperlipidemia (LDL-C >190 mg/dl) and aggressive lipid targets, a 20 mg starting dose may be considered. *Homozygous Familial Hypercholesterolemia:* The recommended starting dose of COUGAR is 20 mg once daily in patients with homozygous FH. Response to therapy should be estimated from pre-apheresis LDL-C levels. *Use with Cyclosporine or Lopinavir/Ritonavir:* In patients taking cyclosporine, therapy should be limited to COUGAR 5 mg once daily. In patients taking a combination of lopinavir and ritonavir, the dose of COUGAR should be limited to 10 mg once daily. *Concomitant Lipid-Lowering Therapy:* The risk of skeletal muscle effects may be enhanced when COUGAR is used in combination with niacin or fenofibrate: a reduction in dose may be considered. The effect of COUGAR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If COUGAR is used in combination with gemfibrozil, the dose of COUGAR should be limited to 10 mg once daily. *Dosage in Patients with Renal Insufficiency:* No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CLcr <30 mL/min/1.73 m2) not on hemodialysis, dosing of COUGAR should be started at 5 mg once daily and not to exceed 10 mg once daily.

SPECIAL INSTRUCTIONS TO THE PHYSICIAN: *Overdosage:* There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

STORAGE/PRECAUTIONS: Store in a cool, dry and dark place between 15-30 °C. Keep all medicines out of the reach of children.

PRESENTATION: COUGAR 5, 10 & 20 mg Tablets are available in packing containing 10 tablets, respectively.

**Scotmann Specs.*

عمومی خوراک: ڈاکٹر کی ہدایت کے مطابق۔ احتیاط: دوا صرف مستند ڈاکٹر کے زیرِ ہدایت استعمال کریں۔ روشنی، نمی اور گرمی سے بچائیں۔ 15 سے 30 ڈگری سینٹی گریڈ کے درمیان محفوظ کریں۔ تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

Complete Medical Information available only for doctors on request.

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