PRESCRIBING INFORMATION (For the use of a Registered Medical Practitioner/a Hospital or Laboratory only)

INTORAS-5/10/20

(Rosuvastatin Tablets 5 mg, 10 mg & 20 mg)

COMPOSITION

Intoras-5

Rosuvastatin Tablets 5 mg

Each film coated tablet contains:

Rosuvastatin Calcium

Eq. to Rosuvastatin 5 mg

Intoras-10

Rosuvastatin Tablets 10 mg

Each film coated tablet contains:

Rosuvastatin Calcium

Eq. to Rosuvastatin 10 mg

Intoras-20

Rosuvastatin Tablets 20 mg

Each film coated tablet contains:

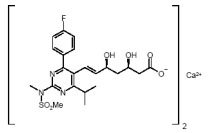
Rosuvastatin Calcium

Eq. to Rosuvastatin 20 mg

DESCRIPTION

Rosuvastatin calcium is a synthetic lipid-lowering agent. It is an 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 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. Its structural formula is:



CLINICAL PHARMACOLOGY

Mechanism of Action:

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. *In vivo* studies in animals, and *in vitro* studies in cultured animal and human cells have shown rosuvastatin to have a high uptake and selectivity for action in the liver, the target organ for cholesterol lowering. In *in vivo* and *in vitro* studies, 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.

Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and nonHDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), nonfamilial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. Rosuvastatin reduces total-C, LDL-C, VLDL-cholesterol (VLDL-C), ApoB, nonHDL-C and TG, and increases HDL-C in patients with isolated hypertriglyceridemia.

Pharmacokinetics:

Absorption: In clinical pharmacology studies in man, peak plasma concentrations of rosuvastatin were reached 3 to 5 hours following oral dosing. Both peak concentration (Cmax) 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 did not affect the AUC of rosuvastatin.

Distribution: 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.

Metabolism: 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.

Excretion: Following oral administration, rosuvastatin and its metabolites are primarily excreted in the faeces (90%). The elimination half-life ($t_{1/2}$) of rosuvastatin is approximately 19 hours. After an intravenous dose, approximately 28% of total body clearance was via the renal route, and 72% by the hepatic route.

Special Populations

Race: A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic, and Black or Afro-Caribbean groups. Pharmacokinetic studies have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls. Rosuvastatin dosage should be adjusted in Asian patients

Gender: There were no differences in plasma concentrations of rosuvastatin between men and women.

Geriatric: There were no differences in plasma concentrations of rosuvastatin between the nonelderly and elderly populations (age ³ 65 years).

Paediatric: In a pharmacokinetic study, 18 patients (9 boys and 9 girls) 10 to 17 years of age with heterozygous FH received single and multiple oral doses of rosuvastatin. Both C_{max} and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Renal Insufficiency: Mild to moderate renal impairment (creatinine clearance ³ 30 mL/min/1.73m²) had no influence on plasma concentrations of rosuvastatin. However, plasma concentrations of rosuvastatin increased to a clinically significant extent (about 3-fold) in patients with severe renal impairment (CLcr< 30 mL/min/1.73m²) not receiving dialysis compared with healthy subjects (CLcr > 80 mL/min/1.73m²).

Hemodialysis: Steady-state plasma concentration of rosuvastatin in patients on chronic hemodialysis were approximately 50% greater compared with healthy volunteer subjects with normal renal function.

Hepatic Insufficiency: Rosuvastatin is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of hepatic transaminase levels. Chronic alcohol liver disease is known to increase rosuvastatin exposure; rosuvastatin should be used with caution in these patients.

INDICATIONS AND USAGE

Rosuvastatin is indicated for

1. Patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and triglyceride levels and to increase HDL-C.
2. Patients with hypertriglyceridemia as an adjunct to diet.
3. Patients with primary dysbetalipoproteinemia (Type III hyper lipoproteinemia) as an adjunct to diet.
4. Patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, total-C, and ApoB.
5. Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet.
6. Pediatric patients of 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy.

Prior to initiating therapy with rosuvastatin, secondary causes for hypercholesterolemia (e.g., poorly-controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysliposproteinemias, obstructive liver disease, other drug therapy, and alcoholism) should be excluded, and a lipid profile should be performed to measure total-C, LDL-C, HDL-C and TG.

DOSAGE AND ADMINISTRATION

Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)

The dose range for rosuvastatin is 5 to 40 mg once daily. Therapy with rosuvastatin should be individualized according to goal of therapy and response. The usual recommended starting dose of rosuvastatin is 10 mg once daily. After initiation and/or upon titration of rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolemia

The recommended starting dose of rosuvastatin is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. Rosuvastatin should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis)

Dosage in patients taking cyclosporine

In patients taking cyclosporine, therapy should be limited to rosuvastatin 5 mg once daily.

Dosage in patients with renal insufficiency

For patients with severe renal impairment (CLcr <30 mL/min/1.73 m²) not on hemodialysis, dosing of rosuvastatin should be started at 5 mg once daily and not to exceed 10 mg once daily.

Paediatric Patients (10 to 17 years of age)

The usual dose range of rosuvastatin is 5-20 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in this patient population).

CONTRAINDICATIONS:

Rosuvastatin is contraindicated in patients with a known hypersensitivity to it.

Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases.

Pregnancy and Lactation:

HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. Rosuvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus.

WARNING & PRECAUTIONS:

Liver Enzyme abnormalities

HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy.

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. If increase in ALT or AST of >3 times of upper limit of normal (ULN) persists, reduction of dose or withdrawal of rosuvastatin is recommended.

Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin.

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose (40 mg). Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy (e.g. age ≥65 years, inadequately treated hypothyroidism, renal impairment. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, cyclosporine, lopinavir/ritonavir, or atazanavir/ritonavir. Rosuvastatin should be discontinued if marked elevated creatinine kinase levels occur or myopathy is diagnosed or suspected. Rosuvastatin therapy should be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, dehydration, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, or uncontrolled seizures). All patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Renal Failure

Administration of rosuvastatin 20 mg to patients with severe renal impairment (CLcr <30 mL/min/1.73 m²) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers.

Endocrine Function

Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if rosuvastatin is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

Pregnancy (Category X)

Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety of rosuvastatin in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

Nursing Mothers

It is not known whether rosuvastatin is excreted in human milk, but a small amount of another drug in this class does pass into breast milk. In rats, breast milk concentrations of rosuvastatin are three times higher than plasma levels; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because HMG-CoA reductase inhibitors have a potential to cause serious adverse reactions in nursing infants, women who require rosuvastatin treatment should be advised not to nurse their infants.

Paediatric Use

The safety and effectiveness of rosuvastatin in patients with 10 to 17 years of age with heterozygous familial hypercholesteremia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5 mg, 10 mg, and 20 mg daily rosuvastatin had an adverse experience profile generally similar to that of treated with placebo.

ADVERSE REACTIONS:

The following serious adverse reactions are discussed in detail in WARNINGS section:

- Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy
- Liver enzyme abnormalities

The most commonly reported adverse reactions (incidence ≥2%) in the rosuvastatin controlled clinical trial database of 5394 patients were: headache, myalgia, abdominal pain, asthenia and nausea. Other adverse reactions reported were dizziness, hypersensitivity (including rash, pruritus, urticaria, and angioedema) and pancreatitis.

Reported laboratory abnormalities were dipstick-positive proteinuria and microscopic hematuria; elevated creatine phosphokinase, transaminases, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin; and thyroid function abnormalities.

The following adverse reactions have been identified during postapproval use of rosuvastatin: arthralgia, hepatic failure, hepatitis, jaundice, memory loss, depression, and sleep disorders (including insomnia and nightmares).

In JUPITER study, there was a significantly higher frequency of diabetes reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%).Mean HbA1C was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo.

DRUG INTERACTIONS:

Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P4503A4 inhibitors (ketoconazole, erythromycin, itraconazole).

Cyclosporine: Cyclosporine significantly increased rosuvastatin exposure. Therefore, in patients taking cyclosporine, therapy should be limited to rosuvastatin 5 mg once daily.

Gemfibrozil: Gemfibrozil significantly increased rosuvastatin exposure. Therefore, combination therapy with rosuvastatin and gemfibrozil should be avoided. If used, do not exceed rosuvastatin 10 mg once daily.

Protease Inhibitors: Co-administration of rosuvastatin with certain protease inhibitors given in combination with ritonavir has differing effects on rosuvastatin exposure. The protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin exposure (AUC) up to three-fold For these combinations the dose of rosuvastatin should be limited to 10 mg. The combinations of tipranavir/ritonavir or fosamprenavir/ritonavir produce little or no change in rosuvastatin exposure. Caution should be exercised when rosuvastatin is co-administered with protease inhibitors given in combination with ritonavir.

Coumarin Anticoagulants: rosuvastatin significantly increased INR in patients receiving coumarin anticoagulants. Therefore, caution should be exercised when coumarin anticoagulants are given in conjunction with rosuvastatin. In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs.

Niacin: The risk of skeletal muscle effects may be enhanced when rosuvastatin is used in combination with niacin; a reduction in rosuvastatin dosage should be considered in this setting.

Fenofibrate: When rosuvastatin was coadministered with fenofibrate, no clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates should be carefully weighed against the potential risks of this combination

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:

Store below 30°C, protect from light & moisture

PRESENTATION:

Rosuvastatin tablets are available in blister of 10 tablets.

Manufactured by :

INTAS

INTAS PHARMACEUTICALS LTD.

Camp Road, Selaqui, Dehradun, Uttarakhand, India

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