SINLIP®
ROSUVASTATIN 5 - 10 and 20 mg

Film-coated tablets

POM
Made in Argentina

COMPOSITION
Each film-coated tablet of SINLIP® 5 mg contains:
Rosuvastatin (as rosuvastatin calcium) .....5 mg
Excipients: microcrystalline cellulose, poloxamer, colloidal silicon dioxide, crosspovidone, vegetal magnesium stearate, red ferric oxide, Opadry white YS-1 and Opaglos AG-7350 .....q.s.
Each film-coated tablet of SINLIP® 10 mg contains:
Rosuvastatin (as rosuvastatin calcium) .....10 mg
Ludipress®, colloidal silicon dioxide, poloxamer, vegetal magnesium stearate, Opadry white YS-1, red ferric oxide and Opaglos AG-7350 .....q.s.
Each film-coated tablet of SINLIP® 20 mg contains:
Rosuvastatin (as rosuvastatin calcium) .....20 mg
Ludipress®, colloidal silicon dioxide, poloxamer, vegetal magnesium stearate, Opadry white YS-1, red ferric oxide and Opaglos AG-7350 .....q.s.

THERAPEUTIC ACTION
Lipid-lowering agent.

INDICATIONS
SINLIP® is indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL cholesterol (LDL-C), apolipoprotein B (ApoB), non-HDL cholesterol (non-HDL-C) and triglycerides (TG) and to increase HDL cholesterol (HDL-C) in adult patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia (Fredrickson type IIa and IIb), when response to diet and other non-pharmacological interventions (such as exercise and weight reduction) is inadequate.
SINLIP® is also indicated as an adjunct to diet for the treatment of adult patients with hypertriglyceridemia (Fredrickson type IV).
SINLIP® is also indicated as an adjunct to diet and other lipid-lowering treatments (e.g., LDL apheresis), or alone if such treatments are unavailable, to reduce LDL-C, Total-C and ApoB in adult patients with homozygous familial hypercholesterolemia.
SINLIP® is also indicated as an adjunct to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower Total-C and LDL-C.
Before starting treatment with SINLIP®, secondary causes of hypercholesterolemia must be ruled out.

CLINICAL PHARMACOLOGY
Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early precursor in cholesterol biosynthesis. Rosuvastatin has high uptake into and selectivity for the liver, the target organ for cholesterol lowering. Rosuvastatin increases the number of hepatic LDL receptors on the cell surface, thereby enhancing uptake and catabolism of LDL, and inhibits hepatic synthesis of VLDL, which reduces the total number of VLDL and LDL particles.
Rosuvastatin reduces elevated LDL-C, Total-C and TG and increases HDL-C. It also reduces ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases apolipoprotein AI (ApoA-I). Rosuvastatin also lowers the LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C and the ApoB/ApoA-I ratios. Therapeutic response is obtained within the first week of treatment with rosuvastatin and 90% of maximum response is achieved after two weeks. The maximum response is usually achieved within four weeks and is maintained during long-term therapy.

PHARMACOKINETICS
Absorption. Peak plasma concentrations of rosuvastatin are reached approximately 5 hours following oral dosing. The absolute bioavailability of rosuvastatin is approximately 20%. The efficacy of rosuvastatin is not affected by coadministration with food or by the time of day of drug administration.
Distribution. Rosuvastatin is mainly taken up by the liver, the primary site for cholesterol synthesis and LDL-C clearance. The mean volume of distribution of rosuvastatin at steady-state is approximately 134 liters. Rosuvastatin is approximately 90% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.
Metabolism. Rosuvastatin is not extensively metabolized (only approximately 10%). The major metabolite is N-desmethyl rosuvastatin, which is formed primarily by cytochrome P450 2C9 and is approximately 50% less active than rosuvastatin. There is also a lactone metabolite that is considered clinically inactive. More than 90% of the active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.
Excretion. Approximately 90% of rosuvastatin and its metabolites are excreted in the feces and the remaining 10% is excreted in urine. The elimination half-life of rosuvastatin is approximately 19 hours and it does not increase at higher doses.

DOSAGE AND ADMINISTRATION
Before starting treatment with SINLIP®, the patient should be placed on a cholesterol-lowering diet that should continue during treatment. When initiating SINLIP® therapy, the appropriate starting dose should first be used and only adjusted to the next dose level after four weeks if necessary, according to the patient's response and individualized goal of therapy, using current consensus guidelines. The dose range for SINLIP® is 5 to 40 mg orally once daily. The 40 mg dose should only be used for those patients with severe hypercholesterolemia and high cardiovascular risk who have not achieved their treatment goal with the 20 mg dose.
The usual starting dose is 10 mg once daily. A 5 mg once daily starting dose should be considered in the following cases: patients who require less aggressive LDL-C lowering; patients who have predisposing factors for

myopathy; Asian patients; concomitant treatment with cyclosporine, patients with severe renal impairment not on hemodialysis. (See WARNINGS). For patients with marked hyperlipidemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20 mg once daily starting dose may be considered.
For patients with homozygous familial hypercholesterolemia, a starting dose of 20 mg once daily and a maximum dose of 40 mg once daily are recommended.
Therapeutic response is obtained within the first two weeks of rosuvastatin treatment. Maximum response is usually seen after four weeks and maintained during treatment. After initiation of SINLIP® therapy or upon titration, lipid levels should be analyzed within two to four weeks and the dosage adjusted accordingly.
SINLIP® may be administered at any time of day, with or without food.

CONTRAINDICATIONS

SINLIP® is contraindicated in patients with: a known hypersensitivity to any component of this product; active liver disease, which may include unexplained persistent elevations of serum transaminases and any elevation of serum transaminases that exceeds 3 times the upper limit of normal.
SINLIP® is also contraindicated in women who are or may become pregnant and in nursing mothers. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, SINLIP® may cause fetal harm when administered to pregnant women and serious adverse reactions in nursing infants when administered to nursing mothers. It is not known whether rosuvastatin is excreted in human milk. The safety of rosuvastatin in lactation has not been established.

WARNINGS

Liver enzyme abnormalities and monitoring:
Because HMG-CoA reductase inhibitors may cause biochemical alterations of liver function, it is recommended that liver function tests be performed before and at three months following the initiation of therapy with SINLIP® or any elevation of dose, and periodically (e.g., every six months) thereafter. The incidence of persistent elevations in serum transaminases (> 3 times the upper limit of normal (ULN) on two consecutive measurements) in fixed dose studies was 0.4, 0, 0 and 0.1 for the 5, 10, 20 and 40 mg rosuvastatin doses, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. If an increase in serum transaminases greater than 3 times ULN persists, SINLIP® should be withdrawn or the dose reduced. Increases in serum transaminases are usually seen during the first three months of treatment.
Skeletal muscle effects:
As with other HMG-CoA reductase inhibitors, effects on skeletal muscle such as uncomplicated myalgia, myopathy, and, rarely, rhabdomyolysis and acute renal failure secondary to myoglobinuria have been reported in patients taking rosuvastatin. Creatine kinase (CK) elevations have also been reported in 0.2 to 0.4% of patients taking rosuvastatin at doses up to 40 mg in clinical studies. CK levels should be monitored during treatment with rosuvastatin. Rhabdomyolysis is rare but more frequent at higher doses. Myopathy (muscle pain or weakness in conjunction with increases in CK values > 10 times ULN) was reported in approximately 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. SINLIP® should be prescribed with caution in patients with predisposing factors for myopathy (e.g., renal impairment, hypothyroidism, age ≥ 65 years). All patients should be advised to promptly report unexplained muscle pain or weakness, particularly if accompanied by malaise or fever. CK levels should be measured in these patients and SINLIP® therapy discontinued if CK levels are markedly elevated (>10 times ULN) or if myopathy is diagnosed or suspected.
The risk of myopathy may be increased in circumstances which increase rosuvastatin drug levels. (See PRECAUTIONS).
Although there was no evidence in clinical trials of increased skeletal muscle effects in patients dosed with rosuvastatin and concomitant therapy, an increase in the incidence of myositis and myopathy has been observed in patients receiving other HMG-CoA reductase inhibitors and fibric acid derivatives including fibrates, gemfibrozil, cyclosporine, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics.
SINLIP® 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 or electrolyte disorders, or uncontrolled seizures).
Race:
Pharmacokinetic studies have shown an increase in median exposure to rosuvastatin in Asian subjects when compared to Caucasian subjects. SINLIP® dosing in Asian patients should be started at 5 mg once daily and the possibility of increasing such dose should be carefully studied.
Proteinuria and hematuria
Proteinuria, detected by dipstick testing and mostly tubular in origin, and microscopic hematuria have been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg. Proteinuria was usually transient and not associated with worsening renal function.
Severe renal impairment:
For patients with severe renal impairment (CLcr <30 mL/min/1.73 m2) who do not require hemodialysis, SINLIP® dosing should be started at 5 mg once daily and not exceed 10 mg once daily.
Severe hepatic impairment:
Increased systemic exposure has been observed in patients with severe hepatic impairment, so rosuvastatin dose should not exceed 20 mg once daily.

PRECAUTIONS

As with other HMG-CoA reductase inhibitors, SINLIP® should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Drug interactions

Vitamin K antagonists: As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g., warfarin) may result in an increase in the International Normalized Ratio (INR). Also, discontinuation or down-titration of rosuvastatin may result in a decrease in INR. Therefore, it is recommended that INR be adequatly monitored in patients receiving such combination therapy.
Gemfibrozil: Concomitant administration of rosuvastatin and gemfibrozil increases systemic exposure to rosuvastatin (2-fold increase in Cmax and AUC). Combination therapy with gemfibrozil should therefore be avoided, but if used, SINLIP® dose should not exceed 10 mg once daily.
Fibrates: When rosuvastatin was coadministered with fenofibrate, no clinically significant changes in the plasma concentration of either drug were observed. However, caution is advised if this combination is used. A pharmacodynamic interaction may occur, and an increase in plasma concentrations of rosuvastatin should not be ruled out. The risk of myopathy may be increased when fenofibrate is given concomitantly with rosuvastatin.
Niacin: There is not enough evidence to ascertain the extent to which plasma concentrations of rosuvastatin are

increased by coadministration with niacin, so caution is advised if this combination is used. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of niacin.
Cyclosporine: During concomitant treatment with cyclosporine, rosuvastatin plasma levels were on average 7 times higher than those observed in healthy volunteers, while plasma concentrations of cyclosporine were unchanged. Therefore, SINLIP® dose should be limited to 5 mg once daily in patients taking cyclosporine.
Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminum and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was administered 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.
Cytochrome P450 enzymes: In vitro and in vivo studies have shown that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes and that rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4).
Erythromycin: Concomitant administration of rosuvastatin and erythromycin resulted in a 20% decrease in the AUC (0-t) and a 30% decrease in the Cmax of rosuvastatin. This interaction may be due to the increase in gut motility caused by erythromycin.
Oral contraceptives: It has been reported that concomitant use of rosuvastatin and an oral contraceptive increased the AUC of ethinyl estradiol and norgestrel by 26% and 34%, respectively. These increased plasma levels should be taken into account when selecting oral contraceptive doses.
Lopinavir/Ritonavir: The risk of myopathy during treatment with SINLIP® may be increased with concurrent administration of lopinavir/ritonavir. In patients taking a combination of lopinavir and ritonavir, SINLIP® dose should be limited to 10 mg once daily.
Carcinogenesis, mutagenesis, impairment of fertility
Preclinical data have not revealed any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity potential. In a rat pre- and postnatal study, reproductive toxicity was evident from reduced litter sizes, litter weight and pup survival. These effects were observed at maternotoxic doses at systemic exposures several times above the therapeutic exposure level.
Pregnancy
SINLIP® is contraindicated in pregnancy (see CONTRAINDICATIONS). There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Studies in rats have shown that rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration. SINLIP® may cause fetal harm when administered to a pregnant woman.
Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the fetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. Women of child bearing potential should use appropriate contraceptive measures. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.
Nursing mothers
Rosuvastatin is excreted in the milk of rats. It is not known whether rosuvastatin is excreted in human milk. Given that another drug in this class passes into human milk, that HMG-CoA reductase inhibitors may cause serious adverse reactions in nursing infants and that the safety of rosuvastatin in lactation has not been established, SINLIP® is contraindicated in nursing mothers. (See CONTRAINDICATIONS).
Pediatric use
The safety and effectiveness of rosuvastatin in pediatric patients have not been established. Therefore, SINLIP® is not recommended for pediatric use. Treatment experience with rosuvastatin is limited to a small number of patients (age ≥ 8 years) with homozygous familial hypercholesterolemia.
Geriatric use
No differences in adverse events were seen between patients aged ≥ 75 years and younger patiens taking rosuvastatin. However, elderly patients are at higher risk of myopathy so SINLIP® should be prescribed with caution in the elderly. A starting dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.
Renal impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥30 mL/min/1.73 m2), but it is increased to a clinically significant extent in patients with severe renal impairment who are not receiving hemodialysis. Therefore, SINLIP® dosing should be started at 5 mg once daily and not exceed 10 mg once daily for patients with severe renal impairment (CLcr <30 mL/min/1.73 m2) who do not require hemodialysis.
Hepatic impairment
There is no evidence of increased exposure to rosuvastatin in subjects with mild to moderate hepatic impairment. However, increased systemic exposure has been observed in subjects with severe hepatic impairment, so rosuvastatin dose should not exceed 20 mg once daily in these patients.
SINLIP® is contraindicated in patients with active liver disease, which may include unexplained persistent elevations of serum transaminases and any elevation of serum transaminases that exceeds 3 times the upper limit of normal. Chronic alcohol liver disease increases rosuvastatin exposure, so SINLIP® should be used with caution in these patients.
Effects on ability to drive and use machines
Rosuvastatin is unlikely to affect the ability to drive vehicles or operate machines.

ADVERSE REACTIONS
The adverse events seen with rosuvastatin are generally mild and transient. As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent. Few cases of rhabdomyolysis were reported in subjects receiving rosuvastatin 80 mg, which were occasionally associated with renal function impairment. All these cases improved when therapy was discontinued.
The most frequent adverse events are (>2%) were: headache, asthenia, myalgia, constipation, nausea and abdominal pain.
The following adverse events were also described. Frequencies are ranked as follows: common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1000); very rare (<1/10,000).
General disorders
Uncommon: chest pain, infection, pelvic pain, neck pain, back pain, cephalea, flu syndrome.
Rare: syncope.
Nervous system disorders
Uncommon: depression, anxiety, paresthesia, vertigo, neuralgia, hypertonia, insomnia and dizziness.

Gastrointestinal disorders
Uncommon: vomiting, flatulence, gastroenteritis, gastritis, diarrhea, dyspepsia and periodontal abscess.
Rare: hepatitis, pancreatitis.
Musculoskeletal, connective tissue and bone disorders
Uncommon: pathological fracture, arthralgia and arthritis.
Rare: myasthenia, myopathy (including myositis) and rhabdomyolysis.
Cardiovascular disorders
Uncommon: hypertension, vasodilation, palpitation, angina pectoris, peripheral edema.
Rare: arrythmia.
Metabolic and nutritional Disorders
Uncommon: diabetes mellitus.
Skin and subcutaneous tissue disorders
Uncommon: ecchymosis, rash, pruritus, urticaria.
Respiratory system disorders
Uncommon: rhinitis, sinusitis, pharyngitis,bronchitis, cough, dyspnea, asthma and pneumonia.
Urogenital System
Uncommon: urinary tract infection.
Rare: renal impairment.
Blood disorders
Uncommon: anemia.
Immune system disorders
Rare: hypersensitivity reactions (including rash, angioedema, facial edema, urticaria, leukopenia, thrombocytopenia), photosensitivity reaction.
Laboratory abnormalities
As with other HMG-CoA reductase inhibitors, dose-related increases in transaminases and CK levels have been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. Dipstick-positive proteinuria, mostly tubular in origin, and microscopic hematuria have been observed in patients treated with higher doses of rosuvastatin, in particular 40 mg.
Shifts in urine protein from none or trace to ++ or more were seen in <1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. Proteinuria was transient or intermittent in most cases and has not been shown to be predictive of acute or progressive renal disease. Rosuvastatin dose should be adjusted if renal disease develops.
Other abnormal laboratory values reported were elevated glucose, glutamyl transpeptidase, alkaline phosphatase and bilirubin levels and altered thyroid function.

OVERDOSE
There is no specific treatment in the event of SINLIP® overdose. The patient should be treated symptomatically and supportive measures instituted as required; liver function and CK levels should be monitored. Hemodialysis does not significantly enhance clearance of rosuvastatin.
In case of overdose, go to the nearest Hospital or call a poison control center.
Initial treatment for overdose: After careful clinical assessment of the patient, the time from ingestion or administration, the amount ingested and the potential contraindication of certain procedures (e.g. induced emesis or gastric lavage, administration of activated charcoal and/or saline purge, etc.), standard supportive measures should be adopted as required.

HOW SUPPLIED
SINLIP® 5 - 10 and 20 mg: packages containing 30 film-coated tablets.

STORAGE
Store in the original package at room temperature; excursions permitted to 15-30°C (59-86ºF).

"KEEP OUT OF THE REACH OF CHILDREN"

Gador
Devoted to People's Health

Gador

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Material Reciclable

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