Rosuvastatin Calcium

Roswin®

5 mg & 10 mg Film-Coated Tablet

HMG-CoA reductase inhibitor / antihyperlipidemic

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FORMULATION
Each film-coated tablet contains:
Rosuvastatin (as calcium) ..... 5 mg or 10 mg

PRODUCT DESCRIPTION
5 mg Tablet: White to off-white, circular, biconvex, film-coated tablet
10 mg Tablet: Pinkish-brown, circular, biconvex, film-coated tablet

CLINICAL PHARMACOLOGY
Pharmacodynamics
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 into, and selectivity for, action in the liver, the target organ for cholesterol lowering.

Rosuvastatin exerts its lipid-modifying effects by increasing the number of hepatic low density lipoprotein (LDL) receptors on the cell surface, thus enhancing uptake and catabolism of LDL and by inhibiting the hepatic synthesis of very low density lipoprotein (VLDL), thereby reducing the total VLDL and LDL particles.

Studies have shown that HMG-CoA reductase inhibitors decrease non-high density lipoprotein (non-HDL), i.e., all circulating cholesterol not in HDL, and apolipoprotein B (Apo B) or reduce the Apo B/Apo A-I ratio.

Pharmacokinetics
Peak rosuvastatin plasma concentrations are reached 3 to 5 hours after oral administration. Both peak concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increase in direct proportion to rosuvastatin dose. The absolute bioavailability of rosuvastatin is approximately 20%.

Administration of rosuvastatin with food did not affect rosuvastatin AUC.

Rosuvastatin AUC does not differ after morning or evening drug administration.

Rosuvastatin's mean volume of distribution at steady-state is about 134 L. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Rosuvastatin is not extensively metabolized; about 10% of a radiolabeled dose is recovered as metabolite. The major metabolite is N-desmethyl rosuvastatin, which is formed principally by cytochrome P450 2C9; *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, more than 90% of active plasma HMG-CoA reductase inhibitory activity is accounted for by rosuvastatin.

Rosuvastatin and its metabolites are primarily excreted in the feces (90%) after oral administration. The elimination half-life ($t_{½}$) is about 19 hours.

Pharmacokinetic studies demonstrate an approximate 2-fold increase in median exposure (AUC and C_{max}) in Asian subjects (having either Vietnamese, Filipino, Chinese, Japanese, Korean, or Asian-Indian origin) compared with Caucasians. A population pharmacokinetic analysis showed no clinically relevant differences in pharmacokinetics among Caucasians, Hispanic and Black or Afro-Caribbean groups (see **WARNINGS AND PRECAUTIONS**).

INDICATIONS
Dyslipidemia
In adult patients, rosuvastatin is indicated to:
- Decrease elevated total cholesterol (total-C), LDL-cholesterol (LDL-C) and triglycerides (TG) and to increase high density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia (Fredrickson types IIa and IIb). Rosuvastatin also decreases Apo B, non-HDL-C, VLDL-C, VLDL-TG, LDL-C/HDL-C, total-C/HDL-C, non-HDL-C/HDL-C, and Apo B/Apo A-I ratios and increases Apo A-I.
- Treat isolated hypertriglyceridemia (Fredrickson type IV hyperlipidemia)
- Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipoproteinemia)
- Decrease total-C and LDL-C in patients with homozygous familial hypercholesterolemia as adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such treatments are unavailable
- Slow the progression of atherosclerosis as part of a treatment strategy to decrease total-C and LDL-C to target levels

In children and adolescent patients 10 to 17 years old, rosuvastatin is indicated to:
- Decrease total-C, LDL-C and Apo B levels in children and adolescents 10 to 17 years old (boys Tanner Stage II and above, and girls who are at least one year post-menarche) with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present:
  LDL-C >190 mg/dL or
  LDL-C >160 mg/dL and:
  - there is a positive family history of premature cardiovascular disease or
  - two or more other cardiovascular risk factors are present in the patient

Primary Prevention of Cardiovascular Disease
In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age (≥50 years old in men and ≥65 years old in women), hsCRP ≥2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, rosuvastatin is indicated to:
- decrease the risk of stroke
- decrease the risk of myocardial infarction
- decrease the risk of arterial revascularization procedures

DOSAGE AND ADMINISTRATION
General Dosing Recommendations
Lipid-altering agents such as rosuvastatin should be used in conjunction with appropriate diet and exercise.

Individualize dose according to goal of therapy and response. Determine lipid levels within 2 to 4 weeks after initiating and/or titrating rosuvastatin therapy and adjust dosage accordingly. Dose adjustment can be made at 2 to 4 weeks intervals.

Adult Dosage Range: 5 to 40 mg/day, given as a single dose at any time of the day, with or without food

Usual Starting Dose: 10 to 20 mg once a day

The 40 mg dose is only recommended for patients with severe hypercholesterolemia at high cardiovascular risk (in particular those with familial hypercholesterolemia), who do not achieve their treatment goal using the 20 mg dose, and in whom routine follow-up will be performed. Physician supervision is recommended when the 40 mg dose is initiated (see **CONTRAINDICATIONS**).

AGE GROUP	INDICATIONS	RECOMMENDED ORAL ROSUVASTATIN DOSE
Adults	Hyperlipidemia (including Heterozygous Familial Hypercholesterolemia), Mixed Dyslipidemia, Isolated Hypertriglyceridemia, Slowing of the Progression of Atherosclerosis	**Initial Dose:** 10 mg once a day - For patients with severe hypercholesterolemia (including heterozygous familial hypercholesterolemia): 20 mg once a day
	Homozygous Familial Hypercholesterolemia	**Usual Initial Dose:** 20 mg once a day - Response to therapy should be estimated from pre-apheresis LDL-C levels
	Primary Prevention of Cardiovascular Disease	**Usual Dose:** 20 mg once a day
Children and adolescents 10 to 17 years old	Heterozygous Familial Hypercholesterolemia	**Usual Initial Dose:** 5 mg once a day **Usual Dose Range:** 5 to 20 mg once a day **Maximum Recommended Dose:** 20 mg once a day - Adjustments should be made at intervals of 4 weeks or more
	Or, as prescribed by a physician.	

Dosage in Asian Patients
Initial Dose: 5 mg once a day
The 40 mg dose is contraindicated in these patients.

Dosage in the Elderly (>70 years old)
Initial Dose: 5 mg once a day

Dosage in Patients taking Ciclosporin
Limit dose to 5 mg once a day.

Dosage in Patients taking Gemfibrozil, Lopinavir/Ritonavir and Atazanavir/Ritonavir
Limit dose to 10 mg once a day.

Dosage in Patients with Renal Impairment
Mild to Moderate Renal Impairment: Usual dose range
Moderate Renal Impairment: 5 mg once a day
The 40 mg dose is contraindicated in these patients.
Severe Renal Impairment: All doses of rosuvastatin are contraindicated.

Dosage in Patients with Hepatic Impairment
Mild to moderate hepatic impairment: Usual dose range
Severe hepatic impairment: 10 mg once a day
Dose above 10 mg once a day should be carefully considered because of increased rosuvastatin exposure.

Dosage in Patients with Predisposing factors to Myopathy
Initial dose: 5 mg once a day
The 40 mg dose is contraindicated in some of these patients.

CONTRAINDICATIONS
- Patients with known hypersensitivity to any component of the product
- Patients with active liver disease including unexplained, persistent elevations in serum transaminases and any serum transaminase elevation exceeding three times the upper limit of normal (ULN)
- Patients with severe renal impairment (creatinine clearance <30 mL/min)
- Patients with myopathy
- Women who are or may become pregnant
- Breastfeeding

Rosuvastatin 40 mg is contraindicated in patients with predisposing factors for myopathy/rhabdomyolysis. Such factors include:
- Moderate renal impairment (creatinine clearance <60 mL/min)
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- Alcohol abuse
- Situations where an increase in plasma rosuvastatin levels may occur
- Asian patients
- Concomitant use of fibrates

WARNINGS AND PRECAUTIONS
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).**

Use with caution in patients with predisposing factors for myopathy (e.g., age ≥65 years, inadequately treated hypothyroidism, renal impairment, situations where an increase in plasma levels may occur).

The risk of myopathy during rosuvasvatin treatment may be increased with concurrent administration of some other lipid-lowering therapies (fibrates or niacin), gemfibrozil, ciclosporin, lopinavir/ritonavir, or atazanavir/ritonavir (see **INTERACTIONS WITH OTHER MEDICAMENTS**).

Discontinue rosuvastatin if markedly elevated creatine kinase (CK) levels occur or myopathy is diagnosed or suspected. Temporarily withhold rosuvastatin therapy 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).

Advise patients taking rosuvastatin to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Liver Enzyme Abnormalities and Monitoring: Perform liver function tests before the initiation of rosuvastatin therapy, and if signs or symptoms of liver injury occur.

Increases in serum transaminases [alanine aminotransferase (ALT), aspartate aminotransferase (AST)] have been reported with HMG-CoA reductase inhibitors, including rosuvastatin. In most cases, elevations were transient and resolved or improved on continued therapy or after a brief interruption of therapy. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. If transaminase levels rise to greater than 3 times the upper limit of normal (ULN) and persist, dose reduction or discontinuation of rosuvastatin is recommended.

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking statins, including rosuvastatin. Promptly interrupt rosuvastatin therapy if serious liver injury with clinical symptoms and/or hyperbilirubinemia or jaundice occurs during treatment. If an alternate etiology is not found, do not restart rosuvastatin.

Use with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Renal Effects: In clinical studies, dip-stick positive proteinuria and microscopic hematuria were observed in patients treated with rosuvastatin. These findings were predominant in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator HMG-CoA reductase inhibitor, although it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, consider dose reduction in patients on rosuvastatin therapy with unexplained persistent proteinuria and/or hematuria during routine urinalysis testing.

Endocrine Effects: Increases in HbA_{1c} and fasting serum glucose levels have been associated with HMG-CoA reductase inhibitors, including rosuvastatin.

Although 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.

Interstitial Lung Disease: Exceptional cases of interstitial lung disease have been observed with some statins, particularly with long-term therapy. Presenting features include dyspnea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). Discontinue statin therapy if it is suspected that a patient has developed interstitial lung disease.

Diabetes Mellitus: Rosuvastatin treatment has been associated with an increased risk of diabetes mellitus in patients with fasting glucose 5.6 to 6.9 mmol/L.

Race: Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians. The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolemia is not adequately controlled at doses up to 20 mg daily. (see **CLINICAL PHARMACOLOGY, *Pharmacokinetics*, CONTRAINDICATIONS**).

INTERACTIONS WITH OTHER MEDICAMENTS
(see **DOSAGE AND ADMINISTRATION**)
Ciclosporin: Significantly increased rosuvastatin exposure. Rosuvastatin dose should be limited to 5 mg once a day if rosuvastatin is coadministered with ciclosporin.
Gemfibrozil: Significantly increased rosuvastatin exposure; thus, combination therapy with rosuvastatin and gemfibrozil should be avoided. If used, do not exceed rosuvastatin 10 mg once a day.
Protease Inhibitors: Protease inhibitor combinations lopinavir/ritonavir and atazanavir/ritonavir increase rosuvastatin AUC up to 3-fold. For these combinations, rosuvastatin dose should be limited to 10 mg once a day.
Coumarin Anticoagulants: Rosuvastatin significantly increased International Normalized Ratio (INR) in patients receiving coumarin anticoagulants. In patients taking coumarin anticoagulants and rosuvastatin concomitantly, determine INR before starting rosuvastatin and after any change in dosage and then regularly thereafter until no significant alteration of INR occurs.
Niacin (≥1 g/day): Increased risk of skeletal muscle effects. Exercise caution when prescribing with rosuvastatin.
Fenofibrate: No clinically significant increase in the AUC of rosuvastatin or fenofibrate was observed. Exercise caution when prescribing fenofibrates with rosuvastatin due to the increased risk of myopathy during treatment with HMG-CoA reductase inhibitors with concomitant use of fenofibrates.
Antacid (Aluminum and Magnesium hydroxide): Decreased rosuvastatin plasma concentrations of about 50%. However, this effect was mitigated when the antacid was given 2 hours after rosuvastatin.
Erythromycin: Decreased rosuvastatin's AUC_{0-24} and C_{max} by 20% and 30%, respectively. This is due to the increase in gut motility caused by erythromycin.
Oral Contraceptives/Hormone Replacement Therapy (HRT): Increased plasma concentrations of ethinyl estradiol and norgestrel by 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses.
Cytochrome P450 Enzymes: Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. No clinically relevant interactions have been observed between rosuvastatin and either fluconazole or ketoconazole. Coadministration of itraconazole and rosuvastatin increased rosuvastatin AUC by 28%, however, this is not clinically significant.
Other Medications: There were no clinically significant interactions with antihypertensive agents, antidiabetic agents, digoxin, and ezetimibe.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
Pregnancy: Pregnancy Category X.
Rosuvastatin is contraindicated in women who are or may become pregnant. The drug may cause fetal harm. If a patient becomes pregnant while taking rosuvastatin, the patient should be apprised of the potential hazard to the fetus and the lack of known clinical benefit with continued rosuvastatin use during pregnancy.

Lactation: It is not known whether rosuvastatin is excreted in human milk. Because of the potential risk to breastfed infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug.

Elderly: Elderly patients are at higher risk of myopathy; rosuvastatin should be used with caution in the elderly.

Children: Experience in pediatric patients 8 to 10 years old with homozygous familial hypercholesterolemia is limited. Rosuvastatin is not recommended in children less than 10 years old.

UNDESIRABLE EFFECTS
Body as a Whole: Asthenia, edema, flu syndrome
Gastrointestinal: Abdominal pain, constipation, diarrhea, dyspepsia, nausea, pancreatitis
Hepatic: Fatal and non-fatal hepatic failure, hepatitis, jaundice
Metabolic, Nutritional, Laboratory: Diabetes mellitus, dipstick-positive proteinuria, microscopic hematuria, thyroid function abnormalities, *elevations in the following:* liver transaminases, CK, glucose, glutamyl transpeptidase, alkaline phosphatase, and bilirubin
Musculoskeletal: Arthralgia, back pain, myalgia, myopathy including myositis, rhabdomyolysis with myoglobinuria and acute renal failure, tendon disorders sometimes complicated by rupture
Nervous: Cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion), depression, dizziness, headache, insomnia, nightmares, paresthesia, polyneuropathy, sexual dysfunction, sleep disturbances
Respiratory: Cough, dyspnea, exceptional cases of interstitial lung disease especially with long-term therapy, pharyngitis, rhinitis, sinusitis
Skin: Hypersensitivity reactions including angioedema, pruritus, rash, urticaria, Stevens-Johnson syndrome
Urogenital: Urinary tract infection

OVERDOSE AND TREATMENT
There is no specific treatment in the event of overdose. In case of overdosage, discontinue rosuvastatin and institute appropriate symptomatic and supportive therapy. Liver function and creatinine levels should be monitored. Hemodialysis is unlikely to be of benefit.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Rosuvastatin calcium (Roswin®) 5 mg Film-Coated Tablet, in flex foil x 10s (box of 30s)
Rosuvastatin calcium (Roswin®) 10 mg Film-Coated Tablet, in flex foil x 10s (box of 30s)

STORE AT TEMPERATURES NOT EXCEEDING 30°C
PROTECT FROM LIGHT AND MOISTURE
KEEP THE PRODUCT OUT OF SIGHT AND REACH OF CHILDREN

Manufactured by Ajanta Pharma Limited
Plot No. B-4/5/6, MIDC, Paithan
Aurangabad 431148
Maharashtra State, India
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No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

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