Front

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SYNERRV ROSUVASTATIN

Rosuvastatin Film-Coated Tablets USP 5 mg, 10 mg, 20 mg

PRODUCT NAME:
SYNERRV ROSUVASTATIN 5 (Rosuvastatin Film-Coated Tablets USP 5 mg)
SYNERRV ROSUVASTATIN 10 (Rosuvastatin Film-Coated Tablets USP 10 mg)
SYNERRV ROSUVASTATIN 20 (Rosuvastatin Film-Coated Tablets USP 20 mg)

NAME AND STRENGTH OF ACTIVE INGREDIENT:
SYNERRV ROSUVASTATIN 5 (Rosuvastatin Film-Coated Tablets USP 5 mg): Rosuvastatin Calcium 5.20mg equivalent to 5mg of Rosuvastatin
SYNERRV ROSUVASTATIN 10 (Rosuvastatin Film-Coated Tablets USP 10 mg): Rosuvastatin Calcium 10.40mg equivalent to 10mg of Rosuvastatin
SYNERRV ROSUVASTATIN 20 (Rosuvastatin Film-Coated Tablets USP 20 mg): Rosuvastatin Calcium 20.80mg equivalent to 20mg of Rosuvastatin

PRODUCT DESCRIPTION:
SYNERRV ROSUVASTATIN 5 (Rosuvastatin Film-Coated Tablets USP 5 mg): Pink 4.50 mm round, biconvex, beveled edge, film-Coated tablets, debossed with 'R5' on one side.
SYNERRV ROSUVASTATIN 10 (Rosuvastatin Film-Coated Tablets USP 10 mg): Pink, 5.50 mm round, biconvex, beveled edge, film-Coated tablets, debossed with 'R10' on one side.
SYNERRV ROSUVASTATIN 20 (Rosuvastatin Film-Coated Tablets USP 20 mg): Pink, 7.00 mm round, biconvex, film-Coated tablets, debossed with 'R20' on one side and plain on other side.

PHARMACODYNAMICS:
Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

Mechanism of action:
Rosuvastatin is a selective, potent 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. Triglycerides (TG) and cholesterol in the liver are incorporated, with apolipoprotein B (ApoB), into very low-density lipoprotein (VLDL) and released into the plasma for delivery to peripheral tissues. VLDL particles are TG-rich. Cholesterol-rich low-density lipoprotein (LDL) is formed from VLDL and is cleared primarily through the high affinity LDL receptor in the liver.

Rosuvastatin produces its lipid-modifying effects in two ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to the liver (reverse cholesterol transport).

The involvement of LDL-C in atherogenesis has been well documented. Epidemiological studies have established that high LDL-C, TG, low HDL-C and ApoA-I have been linked to a higher risk of cardiovascular disease. Intervention studies have shown the benefits on mortality and CV event rates of lowering LDL-C and TG or raising HDL-C. More recent data has linked the beneficial effects of HMG-CoA reductase inhibitors to lowering of non-HDL (i.e., all circulating cholesterol not in HDL) and ApoB or reducing the ApoB/ApoA-I ratio.

Pharmacodynamic effects:
Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 1 and 2).

Rosuvastatin also lowers the LDL-C/HDLC, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.

A therapeutic response to rosuvastatin is evident within 1 week of commencing therapy and 90% of maximum response is usually achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Table 1: Dose response in patients with primary hyper-cholesterolemia (Type IIa and IIb) (Adjusted mean percent change from baseline)

Dose	N	LDL -C	Total -C	HDL -C	TG	nonHDL -C	ApoB	ApoA-I
Placebo	13	-7	-5	3	-3	-7	-3	0
5	17	-45	-33	13	-35	-44	-38	4
10	17	-52	-36	14	-10	-48	-42	4
20	17	-55	-40	8	-23	-51	-46	5
40	18	-63	-46	10	-28	-60	-54	0

Table 2: Dose response in patients with hypertriglyceridemia (Type IIb or Type IV) (Median % change from baseline)

Dose	N	TG	LDL -C	Total -C	HDL -C	nonHDL -C	VLDL -C	VLDL -TG
Placebo	26	1	5	1	-3	2	2	6
5	25	-21	-28	-24	3	-29	-25	-24
10	23	-37	-45	-40	8	-49	-48	-39
20	27	-37	-31	-34	22	-43	-49	-40
40	25	-43	-43	-40	17	-51	-56	-48

Rosuvastatin is effective in a wide variety of patient populations with hypercholesterolaemia, with and without hypertriglyceridemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

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 (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 decreased the rate of drug absorption by 20% as assessed by C_{max}, but there was no effect on the extent of absorption as assessed by 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.

Distribution: Mean volume of distribution at steady-state of rosuvastatin is approximately 134 litres. Rosuvastatin is 88% bound to plasma proteins, mostly albumin. This binding is reversible and independent of plasma concentrations.

Metabolism: Rosuvastatin is not extensively metabolised; approximately 10% of a radiolabelled 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 metabolite are primarily excreted in the faeces (90%). The elimination half-life ($t_{½}$) 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:
Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin.

Paediatric use: The safety and effectiveness of rosuvastatin in patients 10 to 17 years of age with heterozygous familial hypercholesterolemia were evaluated in a controlled clinical trial of 12 weeks duration followed by 40 weeks of open-label exposure. Patients treated with 5mg, 10mg and 20mg daily rosuvastatin had an adverse experience profile generally similar to that of patients treated with placebo. Although not all adverse reactions identified in the adult population have been observed in clinical trials of children and adolescent patients, the same warnings and precautions for adults should be considered for children and adolescents. There was no detectable effect of rosuvastatin on growth, weight, BMI (body mass index), or sexual maturation in paediatric patients (10 to 17 years of age). Adolescent females should be counselled on appropriate contraceptive methods while on rosuvastatin therapy.

Rosuvastatin has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age. Doses of rosuvastatin greater than 20mg have not been studied in the paediatric population.

In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

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 Cmax and AUC of rosuvastatin were similar to values observed in adult subjects administered the same doses.

Genetic polymorphisms: Disposition of HMG-CoA reductase inhibitors, including rosuvastatin, involves OATP1B1 and BCRP transporter proteins. In patients with SLCO1B1 (OATP1B1) and/or ABCG2 (BCRP) genetic polymorphisms there is a risk of increased rosuvastatin exposure. Individual polymorphisms of SLCO1B1 c.521CC and ABCG2 c.421AA are associated with an approximate 1.6-fold higher rosuvastatin exposure (AUC) compared to the SLCO1B1 c.521TT or ABCG2 c.421CC genotypes. This specific genotyping is not established in clinical practice, but for patients who are known to have these types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC in Asian subjects compared with Caucasians. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups.

Patients with renal impairment: Mild to moderate renal impairment (CLcr ≥ 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 haemodialysis compared with healthy subjects (CLcr > 80 mL/min/1.73m²).

INDICATION:
SYNERRV ROSUVASTATIN (rosuvastatin calcium) is indicated as an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol, LDL-cholesterol, ApoB, the total cholesterol: HDL-cholesterol ratio and triglycerides and for increasing HDL-C, in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate including:

- Prevention of Cardiovascular Events. In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, SYNERRV ROSUVASTATIN is indicated to reduce total mortality and the risk of major cardiovascular events (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization)
- SYNERRV ROSUVASTATIN is indicated as an adjunct to diet for the treatment of patients with primary dysbetalipoproteinemia (Type III Hyperlipoprotinemia).
- Primary hypercholesterolaemia (Type IIa including heterozygous familial hypercholesterolaemia and severe non-familial hyper-cholesterolaemia)
- Combined (mixed) dyslipidemia (Type IIb)
- Homozygous familial hypercholesterolaemia where rosuvastatin is used either alone or as an adjunct to diet and other lipid lowering treatment such as apheresis.
- SYNERRV ROSUVASTATIN is indicated 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.
- Paediatric Patients 10 to 17 years of age with Heterozygous Familial Hypercholesterolemia (HeFH): Adjunct to diet to reduce Total-C, LDL-C and ApoB levels in adolescent boys and girls, who are at least one year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolaemia if after an adequate trial of diet therapy the following findings are present: LDL-C > 190mg/dL or > 160mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other CVD risk factors.

RECOMMENDED DOSE:
Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving SYNERRV ROSUVASTATIN (rosuvastatin calcium), and should continue on this diet during treatment with SYNERRV ROSUVASTATIN. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with SYNERRV ROSUVASTATIN, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed. After initiation or upon titration of SYNERRV ROSUVASTATIN, lipid levels should be analysed within 2-4 weeks and the dosage adjusted accordingly.

The usual recommended starting dose of SYNERRV ROSUVASTATIN is 10mg once daily. However, initiation of therapy with 5mg once daily should be considered for special patient populations or patients requiring less aggressive LDL-C reductions. The choice of starting dose should take into account the individual patients' cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions. SYNERRV ROSUVASTATIN may be taken in the morning or evening, with or without food. The majority of patients are controlled at the 10mg dose. However, if necessary, dose adjustments to the next dose level can be made after 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy. Increasing the dose to 40mg should be reserved for patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hyper-cholesterolaemia), who do not achieve their treatment goal on 20mg and should only be initiated under specialist supervision.

The physician who elects to use SYNERRV ROSUVASTATIN at a dose higher than 20mg should periodically re-evaluate the long-term risk/benefit of SYNERRV ROSUVASTATIN for the individual patient. SYNERRV ROSUVASTATIN should be prescribed with caution in patients with pre-disposing factors for myopathy/ rhabdomyolysis.

The dosage of SYNERRV ROSUVASTATIN should be individualised according to baseline LDL-C, total-C/HDL-C ratio and/or TG levels, the recommended target lipid values (see Recommendations for the Management and Treatment of Dyslipidemia [Canada] summarised below in Table 3) and/or the Third Report of the U.S. National Cholesterol Education Program [NCEP Adult Treatment Panel III]) and the patient response.

The majority (80%) of patients treated with rosuvastatin 10mg achieved their NCEP ATP III treatment target for LDL-C levels; fewer subjects (68%) achieved target on the 5mg dose. The difference between rosuvastatin 5mg and 10mg was greatest for high-risk subjects (40% versus 61%, respectively), i.e., for subjects who have a lower LDL-C target.

Lipid levels should be monitored periodically and, if necessary, the dose of SYNERRV ROSUVASTATIN adjusted based on target lipid levels recommended by guidelines.

Table 3: Canadian recommendation for target lipid values based on level of risk

Level of Risk (definition)	Target values LDL-C (mmol/L)	Total-C/ HDL-C ratio	TG (mmol/L)
Very high* (10-year risk of CAD>30%, or history of cardiovascular disease or diabetes)	<2.5	<4.0	<2.0
High* (10-year risk CAD 20%-30%)	<3.0	<5.0	<2.0
Moderate** (10-year risk of CAD 10%-20%)	<4.0	<6.0	<2.0
Low*** (10-year risk of CAD<10%)	<5.0	<7.0	<3.0

* Start medication and lifestyle changes concomitantly if values are bove target values
** Start medication if target values are not achieved after 3 months o f ifestyle modification
*** Start medication if target values are not achieved after 6 months of lifestyle modification

The following reductions in total cholesterol, LDL-C, TG, Total-C/HDL and increases in HDL-C have been observed in a dose-response study, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolaemia:

Table 4: Dose-response in patients with mild to moderate hyper-cholesterolemia (Mean percent change from baseline)

Synerrv Rosuva-statin dose (mg/day)	N	Total-C	LDL-C	TG	HDL-C	Total-C/ HDL-C	Apo B
Placebo	13	-5	-7	-3	3	-8	-3
5	17	-33	-45	-35	13	-41	-38
10	17	-36	-52	-10	14	-43	-42
20	17	-40	-55	-23	8	-44	-46
40	18	-46	-63	-28	10	-51	-54

Dosage in patients with renal insufficiency
The usual dose range applies in patients with mild to moderate renal impairment. For patients with severe renal impairment (CLcr <30 mL/min/1.73 m²) not on haemodialysis, dosing of SYNERRV ROSUVASTATIN should be started at 5mg once daily and not exceed 10mg once daily.

Dosage in patients with hepatic insufficiency
There was no increase in systemic exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in Child-Pugh scores of 8 and 9. In these patients an assessment of renal function should be considered. There is no experience in subjects with Child-Pugh scores above 9. SYNERRV ROSUVASTATIN is contraindicated in patients with active liver disease.

Use in Elderly
The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. The efficacy of rosuvastatin in the geriatric population (≥65 years of age) was comparable to the efficacy observed in the non-elderly.

Paediatric patients (10 to 17 years of age)
In paediatric patients (10 to 17 years of age) with heterozygous familial hypercholesterolemia the usual dose range of SYNERRV ROSUVASTATIN is 5-20mg/day; the maximum recommended dose is 20mg/day (doses greater than 20mg have not been studied in this patient population). Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more.

Use in children below 10 years
The safety and effectiveness in children have not been established. In children and adolescents with homozygous familial hypercholesterolemia experience is limited to eight patients (aged 8 years and above).

Dosage on Asian patients
Initiation of SYNERRV ROSUVASTATIN therapy with 5mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 5, 10 or 20mg once daily.

Genetic polymorphisms
Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of SYNERRV ROSUVASTATIN is recommended.

Dosage in patients with pre-disposing factors to myopathy
The recommended start dose is 5mg in patients with predisposing factors to myopathy.

Concomitant therapy
Rosuvastatin is a substrate of various transporter proteins (e.g., OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when SYNERRV ROSUVASTATIN is administered concomitantly with certain medicinal products that may increase the plasma concentration of rosuvastatin due to interactions with these transporter proteins (e.g., ciclosporin and certain protease inhibitors including combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir. Whenever possible, alternative medications should be considered, and, if necessary, consider temporarily discontinuing SYNERRV ROSUVASTATIN therapy. In situations where co-administration of these medicinal products with SYNERRV ROSUVASTATIN is unavoidable, the benefit and the risk of concurrent treatment and SYNERRV ROSUVASTATIN dosing adjustments should be carefully considered. If concomitant use of SYNERRV ROSUVASTATIN with ciclosporin cannot be avoided, the dose of SYNERRV ROSUVASTATIN should not exceed 5mg once daily.

ROUTE OF ADMINISTRATION:
Oral

CONTRAINDICATIONS:
SYNERRV ROSUVASTATIN is contraindicated:
> in patients with hypersensitivity to rosuvastatin or to any of the excipients.
> in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 times the upper limit of normal (ULN).
> in patients with severe renal impairment (creatinine clearance <30ml/min).
> in patients with myopathy.
> in patients receiving concomitant combination of sofosbuvir /velpatasvir/voxilaprevir
> in patients receiving concomitant ciclosporin.
> during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

WARNINGS AND PRECAUTIONS:
Renal effects
Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, in particular 40mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease. An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg.

Renal impairment
Rosuvastatin exposure is not influenced by mild to moderate renal impairment (CLcr ≥30 mL/min/1.73m²). Exposure to rosuvastatin is increased to a clinically significant extent in patients with severe renal impairment (CLcr <30 mL/min/1.73m²) who are not receiving haemodialysis and dose adjustment is required.

Skeletal Muscle Effects
Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

Effects on skeletal muscle e.g., myalgia, myopathy and, rarely, rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded and caution should be exercised with their combined use. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40mg dose.

Creatine Kinase Measurement
Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the result. If CK levels are significantly elevated at baseline (> 5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment should not be started.

Before Treatment:
SYNERRV ROSUVASTATIN, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
> renal impairment
> hypothyroidism
> personal or family history of hereditary muscular disorders
> previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
> alcohol abuse
> age > 70 years
> situations where an increase in plasma levels may occur
> concomitant use of fibrates

In such patients the risk of treatment should be considered in relation to possible benefit and clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5xULN) treatment should not be started.

Whilst on Treatment:
Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (>5xULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤5xULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing SYNERRV ROSUVASTATIN or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring. Routine monitoring of CK levels in asymptomatic patients is not warranted. There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin. IMNM is clinically characterised by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations.

SYNERRV ROSUVASTATIN should not be used 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, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Table 5: Effect of co-administered medicinal products on rosuva-statin exposure (AUC; in order of decreasing magnitude) from published clinical trials

2-fold or greater than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Sofosbuvir/velpatasvir/ voxilaprevir (400mg-100mg-100mg) + Voxilaprevir (100mg) once daily for 15 days	10mg single dose	7.39-fold ↑
Ciclosporin 75mg BID to 200mg BID, 6 months	10mg OD, 10 days	7.1-fold ↑
Darolutamide 600mg BID, 5 days	5mg, single dose	5.2-fold ↑
Regorafenib 160mg, OD, 14 days	5mg, single dose	3.8-fold ↑
Atazanavir 300mg/ritonavir 100mg OD, 8 days	10mg, single dose	3.1-fold ↑
Simeprevir 150mg OD, 7 days	10mg, single dose	2.8-fold ↑
Velpatasvir 100mg OD	10mg, single dose	2.69-fold ↑
Ombitasvir 25mg/paritaprevir 150mg/ Ritonavir 100mg OD/ dasabuvir 400mg BID	5mg, single dose	2.59-fold ↑
Grazoprevir 200mg/elbasvir 50mg OD	10mg, single dose	2.26-fold ↑
Glecaprevir 400mg/pibrentasvir 120mg OD, 7 days	5mg OD	2.2-fold ↑
Lopinavir 400mg/ritonavir 100mg BID, 17 days	20mg OD, 7 days	2.1-fold ↑
Clopidogrel 300mg loading, followed by 75mg at 24 hours[†]	20mg, single dose[†]	2-fold ↑
Gemfibrozil 600mg BID, 7 days	80mg, single dose	1.9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Eltrombopag 75mg OD, 5 days	10mg, single dose	1.6-fold ↑
Darunavir 600mg/ritonavir 100mg BID, 7 days	10mg OD, 7 days	1.5-fold ↑
Tipranavir 500mg/ritonavir 200mg BID, 11days	10mg, single dose	1.4-fold ↑
Dronedarone 400mg BID	Not available	1.4-fold ↑
Itraconazole 200mg OD, 5 days	10mg, single dose	**1.4-fold ↑
Ezetimibe 10mg OD, 14 days	10mg, OD, 14 days	**1.2-fold ↑
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500mg QID, 7 days	80mg, single dose	20% ↓
Baicalin 50mg TID, 14 days	20mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone. Increase is indicated as "↑", decrease as "↓".
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio
AUC = area under curve; OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

The following medicinal product/combinations did not have a clinically significant effect on the AUC ratio of rosuvastatin at coadministration:
Aleglitazar 0.3mg 7 days dosing; Fenofibrate 67mg 7 days TID dosing; Fluconazole 200mg 11 days OD dosing; Fosamprenavir 700mg/ritonavir 100mg 8 days BID dosing; Ketoconazole 200mg 7 days BID dosing; Rifampin 450mg 7 days OD dosing; Silymarin 140mg 5 days TID dosing.

Other medications: Concurrent use of fibrates may cause severe myositis and myoglobinuria.

Effect of rosuvastatin on co-administered medicinal products
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 or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive resulted in an increase in ethinyl estradiol and norgestrel AUC of 26% and 34%, respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. There are no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT, therefore, a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated.

Other Medicinal Products
Digoxin: Based on data from specific interaction studies no clinically relevant interaction with digoxin is expected.

Paediatric population: Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

PREGNANCY AND LACTATION:
SYNERRV ROSUVASTATIN is contraindicated in pregnancy and lactation.

Women of childbearing potential should use appropriate contraceptive measures.

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, rosuvastatin is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

SIDE EFFECTS:
There have been rare post-marketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

The following adverse events have been reported with some statins:
Sexual dysfunction.
Exceptional cases of interstitial lung disease, especially with long term therapy.
Tendon disorders, sometimes complicated by rupture.
The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40mg dose.

Paediatric patients 10 to 17 years of age: In a 12-week controlled study in boys and post-menarchal girls, the safety and tolerability profile of rosuvastatin 5 to 20mg daily was generally similar to that of placebo.

However, elevations in serum creatine phosphokinase (CK) >10 x ULN were observed more frequently in rosuvastatin compared with placebo-treated children. Four of 130 (3%) children treated with rosuvastatin (2 treated with 10mg and 2 treated with 20 mg) had increased CK >10 x ULN, compared to 0 of 46 children on placebo.

SYMPTOMS AND TREATMENT OF OVERDOSE:
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. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

PHARMACEUTICAL PARTICULARS:
List of Excipients
Tablet Core
Lactose monohydrate, Microcrystalline cellulose, Sodium hydrogen carbonate, Crospovidone, Magnesium stearate (plant origin)
Tablet Coat
Opadry II Pink 32K540023

SHELF LIFE: 24 Months

SPECIAL PRECAUTIONS FOR STORAGE:
Do not store above 30°C. Store in the original package.

PACKAGING AND PACK SIZE:
SYNERRV ROSUVASTATIN tablets come packed within a blister strip made of aluminium cold forming base foil and aluminium lid foil.
- 3 blister strips per box (3 x 10's)
- 10 blister strips per box (10 x 10's)

MANUFACTURER:
Umedica Laboratories Pvt. Ltd.,
Plot No. 221, IInd Phase, G.I.D.C., Vapi, Gujarat, 396195, India.

PRODUCT REGISTRATION HOLDER IN MALAYSIA:
Synerry Sdn. Bhd.,
SO-29-2, Menara 1, KL Eco City,
Jalan Bangsar, Kg. Haji Abdullah Hukum,
59200 Kuala Lumpur, Malaysia

LEAFLET REVISION DATE: 22nd March 2024

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Interactions requiring rosuvastatin dose adjustments (see also Table 5): When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. It is recommended that prescribers consult the relevant product information when considering administration of such products together with rosuvastatin.

If medicinal product is observed to increase rosuvastatin AUC approximately 2-fold or higher, the starting dose of rosuvastatin should not exceed 5mg once daily. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 5mg dose of rosuvastatin with ciclosporin (7.1-fold increase in exposure), a 10mg dose of rosuvastatin with ritonavir/atazanavir combination (3.1-fold increase) and a 20mg dose of rosuvastatin with gemfibrozil (1.9-fold increase).

If medicinal product is observed to increase rosuvastatin AUC less than 2-fold, the starting dose need not be decreased but caution should be taken if increasing the rosuvastatin dose above 20mg.

Protease inhibitors: Coadministration of rosuvastatin with certain protease inhibitors or combination of protease inhibitors may increase the rosuvastatin exposure, (AUC) up to 7-fold. Dose adjustments are needed depending on the level of effect on rosuvastatin exposure.

INTERACTION WITH OTHER MEDICAMENTS:
Effect of co-administered medicinal products on rosuvastatin
Transporter protein inhibitors: Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of rosuvastatin with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy.

Ciclosporin: Ciclosporin increased rosuvastatin exposure and may result in increased risk of myopathy. Therefore, in patients taking ciclosporin, the dose of rosuvastatin should not exceed 5mg once daily

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. For instance, in a pharmacokinetic study, co-administration of 10mg rosuvastatin and a combination product of two protease inhibitors (300mg atazanavir/100mg ritonavir) in healthy volunteers was associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively. The concomitant use of rosuvastatin and some protease inhibitor combinations may be considered after careful consideration of rosuvastatin dose adjustments based on the expected increase in rosuvastatin exposure.

Gemfibrozil and other lipid-lowering products: Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC.

Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (> or equal to 1g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40mg dose is contraindicated with concomitant use of a fibrate. These patients should also start with the 5mg dose. Concurrent use of fibrates may cause severe myositis and myoglobinuria.

Ezetimibe: Concomitant use of 10mg rosuvastatin and 10mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hyper-cholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Antacid: The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50%. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied.

Fusidic acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. As with other statins, muscle related events, including rhabdomyolysis, have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Patients should be closely monitored and temporary suspension of rosuvastatin treatment may be appropriate.

Erythromycin: Concomitant use of rosuvastatin and er