To be sold by retail on prescription of R.M.P. only

ROZUCOR ASP

1. Generic Name

Rosuvastatin and Aspirin Capsules

2. Qualitative and quantitative composition

ROZUCOR ASP-10

Each hard gelatin capsule contains**:**
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin……10mg
(As film coated tablet)
Colours: Red Oxide of Iron and Titanium Dioxide I.P.
Aspirin I.P. ……..… 75mg
(As enteric coated tablet)
Colour: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shells.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Lactose, Hydroxy propyl methyl Cellulose, Triacetin, Titanium dioxide, Ferric oxide red, Stearic acid, Ethyl Cellulose, Diethyl Phthalate, Iso Propyl alcohol, Methlene Chloride, Talc, Triethyl Citrate, Ferric Oxide Yellow, Methacrylic Acid-Ethyl Acrylate Copolymer.

ROZUCOR ASP-20

Each hard gelatin capsule contains**:**
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin……20mg
(As film coated tablet)
Colours: Red Oxide of Iron and Titanium Dioxide I.P.
Aspirin I.P. ……..… 75mg
(As enteric coated tablet)
Colour: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shells.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Lactose, Hydroxy propyl methyl Cellulose, Triacetin, Titanium dioxide, Ferric oxide red, Stearic acid, Ethyl Cellulose, Diethyl Phthalate, Iso Propyl alcohol, Methlene Chloride, Talc, Triethyl Citrate, Ferric Oxide Yellow, Methacrylic Acid-Ethyl Acrylate Copolymer.

ROZUCOR ASP-20/150

Each hard gelatin capsule contains**:**
Rosuvastatin Calcium I.P.
Equivalent to Rosuvastatin…20mg
(As film coated tablet)
Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.
Aspirin I.P. ……..… 150mg
(As enteric coated tablet)

Colour: Yellow Oxide of Iron
Approved colours used in hard gelatin capsule shells.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Lactose, Hydroxy propyl methyl Cellulose, Triacetin, Titanium dioxide, Ferric oxide red, Stearic acid, Ethyl Cellulose, Diethyl Phthalate, Iso Propyl alcohol, Methlene Chloride, Talc, Triethyl Citrate, Ferric Oxide Yellow, Methacrylic Acid-Ethyl Acrylate Copolymer.

3. Dosage form and strength

Dosage form: Hard Gelatin Capsule
Strength: Rosuvastatin 10 and 20 mg, Aspirin I.P 75mg and 150 mg

4. Clinical particulars

4.1 Therapeutic indication

For the treatment of dyslipdemia associated with artherscleroticarterial disease with risk of myocardial infarction, stroke or peripheral vascular disease.

4.2 Posology and method of administration

Dosage: As directed by the physician

Note:

- Not to be used in children below 12 years of age except under medical advice.
- Do not take this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problems to both mother & child.

4.3 Contraindications

- In patients with hypersensitivity to rosuvastatin, salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria) 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 <30 ml/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.
- Active or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia or concurrent anticoagulant therapy.
- Patients who are suffering from gout.
- Severe hepatic impairment.
- Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

4.4 Special warnings and precautions for use

Important: Do not take this product during the last three months of pregnancy unless directed by a doctor. Aspirin taken near the time of delivery may cause bleeding problems to both mother & child**.**

Rosuvastatin

Renal Effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of Rosuvastatin, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease.

Skeletal Muscle Effects

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in Rosuvastatin treated patients with all doses and in particular with doses > 20 mg. Very rare cases of 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.

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

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 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 proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In reported 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.

Rosuvastatin must not be co-administered with systemic formulations of fusidic acid or within 7 days of stopping fusidic acid treatment. In patients where the use of systemic fusidic acid is considered essential, statin treatment should be discontinued throughout the duration of fusidic acid treatment. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving fusidic acid and statins in combination. Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be re-introduced seven days after the last dose of fusidic acid. In exceptional circumstances, where prolonged systemic fusidic acid is needed, e.g. for the treatment of severe infections, the need for co-administration of Rosuvastatin and fusidic acid should only be considered on a case by case basis and under close medical supervision.

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).

Liver Effects

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

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephrotic syndrome, the underlying disease should be treated prior to initiating therapy with Rosuvastatin.

Race

Reported Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians.

Protease Inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin concomitantly with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by use of Rosuvastatin in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin doses in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose of rosuvastatin is adjusted.

Interstitial Lung Disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy. Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes Mellitus

Some evidence suggests that statins as a class raise blood glucose and in some patients, at high risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5.6 to 6.9 mmol/l, BMI >30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

In the reported JUPITER study, the reported overall frequency of diabetes mellitus was 2.8% in rosuvastatin and 2.3% in placebo, mostly in patients with fasting glucose 5.6 to 6.9 mmol/l.

Paediatric Population

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age taking rosuvastatin is limited to a two-year period. After two years of study treatment, no effect on growth, weight, BMI or sexual maturation was detected.

In a reported clinical trial of children and adolescents receiving rosuvastatin for 52 weeks, CK elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently compared to observations in clinical trials in adults.

Aspirin

Caution should be exercised in patients with allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration, since the use of NSAIDs may result in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Aspirin may also precipitate bronchospasm or induce attacks of asthma in susceptible subjects or promote other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly.

Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur.

Aspirin is not recommended during menorrhagia where it may increase menstrual bleeding.

Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological and haemorrhagic effects can occur, and may be severe. Use with caution before surgery, including tooth extraction. Patients should report any unusual bleeding symptoms to their physician.

Care is advised when stopping antiplatelet therapy after stent insertion either after a fixed period of time or in preparation for a planned surgical procedure, as the balance between stent thrombosis and excessive bleeding has to be carefully assessed.

There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason, aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease).

Aspirin is to be used with caution in cases of hypertension and patients with a stomach ulcer or a history of stomach ulcers or duodenal ulcer or haemorrhagic episodes or undergoing therapy with anticoagulants. Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Before commencing long term aspirin therapy for the management of cardiovascular or cerebrovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox.

Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin taken at over dosage.

Aspirin should be avoided in late pregnancy and generally during breast feeding.

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs interactions

Rosuvastatin

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: During concomitant treatment with Rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers. Rosuvastatin is contraindicated in patients receiving concomitant ciclosporin. Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors: Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure. For instance, in a reported pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir/100 mg 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 1 g/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.

Ezetimibe: Concomitant use of 10 mg Rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic 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.

Erythromycin: Concomitant use of Rosuvastatin and erythromycin resulted in a 20% decrease in AUC and a 30% decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes: Results from reported *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. Therefore, drug interactions resulting from cytochrome P450-mediated metabolism are not expected. 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).

Interactions requiring rosuvastatin dose adjustments: When it is necessary to co-administer Rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of Rosuvastatin should be adjusted. The maximum daily dose of Rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of Rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of Rosuvastatin with gemfibrozil (1.9-fold increase), and a 10 mg dose of Rosuvastatin with combination ritonavir/atazanavir (3.1-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

Table 1 Effect of co-administered medicinal products on rosuvastatin 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 (400 mg-100 mg-100 mg) + Voxilaprevir (100 mg) once daily for 15 days	10mg single dose	7.4 -fold ↑
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5mg, single dose	5.2-fold ↑
Regorafenib 160 mg, OD, 14 days	5 mg, single dose	3.8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3.1-fold ↑
Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2.3-fold ↑

Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, 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 75 mg OD, 5 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	**1.4-fold ↑
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	**1.2-fold ↑
Decrease in AUC of rosuvastatin		
Interacting drug dose regimen	**Rosuvastatin dose regimen**	**Change in rosuvastatin AUC***
Erythromycin 500 mg QID, 7 days	80 mg, single dose	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, 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 "↑", no change as "↔", and 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

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.

Fusidic Acid: Interaction studies with rosuvastatin and fusidic acid have not been conducted. The risk of myopathy, including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins. The mechanism of this interaction (whether it is pharmacodynamic or pharmacokinetic, or both) is yet unknown. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination.

If treatment with systemic fusidic acid is necessary, Rosuvastatin treatment should be discontinued throughout the duration of the fusidic acid treatment.

Paediatric population: As per reported data, interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

Aspirin

Contraindicated combinations

Methotrexate (used at doses >15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg Capsules is contraindicated.

Not recommended combinations

Uricosuric agents, e.g. probenecid and sulfinpyrazone:

Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

Combinations requiring precautions for use or to be taken into account

Anticoagulants e.g. coumarin, heparin, warfarin and phenindione:

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

Anti-platelet agents (e.g. clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine):

Increased risk of gastrointestinal bleeding.

Antidiabetics, e.g. sulphonylureas:

Salicylic may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium:

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensive:

NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. Patients with hypertension should be carefully monitored. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency. Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Other non-steroidal anti-inflammatory drugs (NSAIDs):

Concurrent administration can increase side effects. Use of two or more NSAIDs increases risk of gastrointestinal haemorrhage.

Ibuprofen:

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

Ciclosporin, tacrolimus:

Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Systemic Corticosteroids:

The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticosteroids are co-administered. Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids.

Methotrexate (used at doses <15 mg/week):

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Carbonic anhydrase inhibitors:

Reduced excretion of acetazolamide; salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

Antacids and adsorbents:

The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption. Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

Mifepristone:

The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

Alcohol:

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

Antiemetics:

Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

Anti-epileptics:

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered. Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

Leukotriene antagonists:

The plasma concentration of zafirlukst is increased.

Antibacterial:

The toxicity of sulphonamides may be increased.

Thyroid function tests:

Aspirin may interfere with thyroid function tests.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Rosuvastatin

Rosuvastatin is contraindicated in pregnancy and lactation.

Women of child bearing 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. Animal studies provide limited evidence of reproductive toxicity. 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.

Aspirin

Pregnancy

Low doses (up to 100 mg/day):

Clinical studies indicate that doses up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe.

Doses of 100- 500 mg/day:

There is insufficient clinical experience regarding the use of doses above 100 mg/day up to 500 mg/day. Therefore, the recommendations below for doses of 500 mg/day and above apply also for this dose range.

Doses of 500 mg/day and above:

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);

- Renal dysfunction, which may progress to renal failure with oligo- hydroamniosis the mother and the neonate, at the end of pregnancy, to:

- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.

- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of pregnancy.

Breastfeeding

Low quantities of salicylates and of their metabolites are excreted into the breast milk. Since adverse effects for the infant have not been reported up to now, short-term use of the recommended dose does not require suspending lactation. In cases of long-term use and/or administration of higher doses, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

Studies to determine the effect of ROZUCOR ASP on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, ROZUCOR ASP is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that dizziness may occur during treatment.

4.8 Undesirable effects

The adverse reactions seen are generally mild and transient.

Tabulated list of adverse reactions

Based on data from reported clinical studies and extensive post-marketing experience, the following table presents the adverse reaction profile for rosuvastatin and aspirin. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

The frequencies of adverse reactions are ranked according to the following convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Table 2. Adverse reactions based on data from clinical studies and post-marketing experience

System organ class	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders	Increased bleeding tendencies.		Thrombocytopenia Granulocytosis, aplastic anaemia.		Cases of bleeding with prolonged bleeding time such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, haematoma, cerebral haemorrhage and gingival bleeding. Symptoms may persist for a period of 4–8 days after Rozucor Asp

					discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Aspirin decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses). Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
Immune system disorders			Hypersensitivity reactions including angioedema Skin rashes, urticarial, asthma, bronchospasm, angio-oedema, allergic oedema, anaphylactic reactions including shock.		
Endocrine disorders	Diabetes mellitus[1]				Hyperuricemia
Psychiatric disorders					Depression

Nervous system disorders	Headache Dizziness			Polyneuropathy Memory loss Intracranial haemorrhage. Headache, vertigo.	Peripheral neuropathy Sleep disturbances (including insomnia and nightmares)
Respiratory, thoracic and mediastinal disorders		Rhinitis, dyspnoea.	Bronchospasm, asthma attacks.		Cough Dyspnoea
Gastro-intestinal disorders	Constipation Nausea Abdominal pain Dyspepsia		Pancreatitis Severe gastrointestinal haemorrhage, nausea, vomiting, gastritis.		Diarrhoea Gastric or duodenal ulcers and perforation, diarrhoea.
Hepatobiliary disorders			Increased hepatic transaminases	Jaundice Hepatitis	Hepatic insufficiency
Skin and subcutaneous tissue disorders		Pruritus Rash Urticaria	Lyells syndrome, purpura, erythema nodosum, erythema multiforme.		Stevens-Johnson syndrome
Musculo-skeletal and connective tissue disorders	Myalgia		Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture	Arthralgia	Tendon disorders, sometimes complicated by rupture Immune-mediated necrotising myopathy
Renal and urinary disorders				Haematuria	

Reproductive system and breast disorders			Menorrhagia	Gynaecomastia	
General disorders and administration site conditions	Asthenia				Oedema
[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI >30 kg/m^2, raised triglycerides, history of hypertension).					

As with other HMG-CoA reductase inhibitors, the incidence of adverse drug reactions tends to be dose dependent.

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with Rosuvastatin. 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. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with Rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in Rosuvastatin-treated patients with all doses and in particular with doses > 20 mg.

A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued.

Liver effects: As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.

The following adverse events have been reported with some statins:

Sexual dysfunction.

Exceptional cases of interstitial lung disease, especially with long term therapy. The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

Paediatric population: Creatine kinase elevations >10xULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-

week clinical trial of children and adolescents compared to adults. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 OVERDOSE

Rosuvastatin

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.

Aspirin

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, and sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation.

Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

Treatment

Give activated charcoal if an adult present within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten

years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

5. Pharmacological properties

5.1 Mechanism of Action

Rosuvastatin

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 for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin 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.

Acetylsalicylic acid

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions.

Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

5.2 Pharmacodynamicproperties

Rosuvastatin

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

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

Table 3 Dose response in patients with primary hypercholesterolaemia (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

In a reported study a therapeutic effect is obtained within 1 week following treatment initiation and 90% of maximum response is achieved in 2 weeks. The maximum response is usually achieved by 4 weeks and is maintained after that.

Clinical efficacy and safety

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex or age and in special populations such as diabetics or patients with familial hypercholesterolaemia.

From pooled phase III data, Rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (mean baseline LDL-C about 4.8 mmol/L) to recognised European Atherosclerosis Society (EAS; 1998) guideline targets; about 80% of patients treated with 10 mg reached the EAS targets for LDL-C levels (<3 mmol/L).

As per reported data, in a large study, 435 patients with heterozygous familial hypercholesterolaemia were given Rosuvastatin from 20 mg to 80 mg in a force-titration design. All doses showed a beneficial effect on lipid parameters and treatment to target goals. Following titration to a daily dose of 40 mg (12 weeks of treatment), LDL-C was reduced by 53%. Thirty-three percent (33%) of patients reached EAS guidelines for LDL-C levels (<3 mmol/L).

In a force-titration, reported open label trial, 42 patients (including 8 paediatric patients) with homozygous familial hypercholesterolaemia were evaluated for their response to Rosuvastatin 20 – 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In reported clinical studies with a limited number of patients, Rosuvastatin has been shown to have additive efficacy in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

In a reported multi-centre, double-blind, placebo-controlled clinical study (METEOR), 984 patients between 45 and 70 years of age and at low risk for coronary heart disease (defined as Framingham risk <10% over 10 years), with a mean LDL-C of 4.0 mmol/L (154.5 mg/dL), but with subclinical atherosclerosis (detected by Carotid Intima Media Thickness) were randomised to 40 mg rosuvastatin once daily or placebo for 2 years. Rosuvastatin significantly slowed the rate of progression of the maximum CIMT for the 12 carotid artery sites compared to placebo by -0.0145 mm/year [95% confidence interval -0.0196, -0.0093; p<0.0001]. The change from baseline was -0.0014 mm/year (-0.12%/year (non-significant)) for rosuvastatin compared to a progression of +0.0131 mm/year (1.12%/year (p<0.0001)) for placebo. No direct correlation between CIMT decrease and reduction of the risk of cardiovascular events has yet been demonstrated. The population studied in METEOR is low risk for coronary heart disease and does not represent the target population of Rosuvastatin 40 mg. The 40 mg dose should only be prescribed in patients with severe hypercholesterolaemia at high cardiovascular risk.

In the Justification for the Use of Statins in Primary Prevention: An a reported Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events was assessed in 17,802 men (≥50 years) and women (≥60 years).

Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years.

LDL-cholesterol concentration was reduced by 45% (p<0.001) in the rosuvastatin group compared to the placebo group.

In a post-hoc analysis of a high-risk subgroup of subjects with a baseline Framingham risk score >20% (1558 subjects) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.028) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate per 1000 patient-years was 8.8. Total mortality was unchanged in this high-risk group (p=0.193). In a post-hoc analysis of a high-risk subgroup of subjects (9302 subjects total) with a baseline SCORE risk ≥5% (extrapolated to include subjects above 65 yrs) there was a significant reduction in the combined end-point of cardiovascular death, stroke and myocardial infarction (p=0.0003) on rosuvastatin treatment versus placebo. The absolute risk reduction in the event rate was 5.1 per 1000 patient-years. Total mortality was unchanged in this high-risk group (p=0.076).

In the JUPITER trial, there were 6.6% of rosuvastatin and 6.2% of placebo subjects who discontinued use of study medication due to an adverse event. The most common adverse events that led to treatment discontinuation were: myalgia (0.3% rosuvastatin, 0.2% placebo), abdominal pain (0.03% rosuvastatin, 0.02% placebo) and rash (0.02% rosuvastatin, 0.03% placebo). The most common adverse events at a rate greater than or equal to placebo were urinary tract infection (8.7% rosuvastatin, 8.6% placebo), nasopharyngitis (7.6% rosuvastatin, 7.2% placebo), back pain (7.6% rosuvastatin, 6.9% placebo) and myalgia (7.6% rosuvastatin, 6.6% placebo).

Paediatric population

In a reported double-blind, randomised, multi-centre, placebo-controlled, 12-week study (n=176, 97 males and 79 female) followed by a 40-week (n=173, 96 males and 77 female), open-label, rosuvastatin dose-titration phase, patients 10 to 17 years of age (Tanner stage II-V, females at least 1-year post-menarche) with heterozygous familial hypercholesterolaemia received rosuvastatin 5, 10 or 20 mg or placebo daily for 12 weeks and then all received rosuvastatin daily for 40 weeks. At study entry, approximately 30% of the patients were 10 to 13 years and approximately 17%, 18%, 40%, and 25% were Tanner stage II, III, IV, and V, respectively.

LDL-C was reduced 38.3%, 44.6%, and 50.0% by rosuvastatin 5, 10 and 20 mg, respectively, compared to 0.7% for placebo.

At the end of the 40-week, open-label, titration to goal, dosing up to a maximum of 20 mg once daily, 70 of 173 patients (40.5%) had achieved the LDL-C goal of less than 2.8 mmol/L.

After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. This trial (n=176) was not suited for comparison of rare adverse drug events.

As per reported data, rosuvastatin was also studied in a 2-year open-label, titration-to-goal study in 198 children with heterozygous familial hypercholesterolaemia aged 6 to 17 years (88 males and 110 female, Tanner stage <II-V). The starting dose for all patients was 5 mg rosuvastatin once daily. Patients aged 6 to 9 years (n=64) could titrate to a maximum dose of 10 mg once daily and patients aged 10 to 17 years (n=134) to a maximum dose of 20 mg once daily.

After 24 months of treatment with rosuvastatin, the LS mean percent reduction from the baseline value in LDL-C was -43% (Baseline: 236 mg/dL, Month 24: 133 mg/dL). For each age group, the LS mean percent reductions from baseline values in LDL-C were -43% (Baseline: 234 mg/dL, Month 24: 124 mg/dL), -45% (Baseline: 234 mg/dL, Month 24: 124 mg/dL) and -35% (Baseline: 241 mg/dL, Month 24: 153 mg/dL) in the 6 to <10, 10 to <14, and 14 to <18 age groups, respectively.

Rosuvastatin 5 mg, 10 mg, and 20 mg also achieved statistically significant mean changes from baseline for the following secondary lipid and lipoprotein variables: HDL-C, TC, non-HDL-C, LDL-C/HDL-C, TC/HDL-C, TG/HDL-C, non-HDL C/HDL-C, ApoB, and ApoB/ApoA-1. These changes were each in the direction of improved lipid responses and were sustained over 2 years.

No effect on growth, weight, BMI or sexual maturation was detected after 24 months of treatment.

As per reported data, rosuvastatin was studied in a randomised, double-blind, placebo-controlled, multi-centre, cross-over study with 20 mg once daily versus placebo in 14 children and adolescents (aged from 6 to 17 years) with homozygous familial hypercholesterolaemia. The study included an active 4-week dietary lead-in phase during which patients were treated with rosuvastatin 10 mg, a cross-over phase that consisted of a 6-week treatment period with rosuvastatin 20 mg preceded or followed by a 6-week placebo treatment period, and a 12-week maintenance phase during which all patients were treated with rosuvastatin 20 mg. Patients who entered the study on ezetimibe or apheresis therapy continued the treatment throughout the entire study.

A statistically significant (p=0.005) reduction in LDL-C (22.3%, 85.4 mg/dL or 2.2 mmol/L) was observed following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. Statistically significant reductions in Total-C (20.1%, p=0.003), non-HDL-C (22.9%, p=0.003) and ApoB (17.1%, p=0.024) were observed. Reductions were also seen in TG, LDL-C/HDL-C, Total-C/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-1 following 6 weeks of treatment with rosuvastatin 20 mg versus placebo. The reduction in LDL-C after 6 weeks of treatment with rosuvastatin 20 mg following 6 weeks of treatment with placebo was maintained over 12 weeks of continuous therapy. One patient had a further reduction in LDL-C (8.0%), Total-C (6.7%) and non-HDL-C (7.4%) following 6 weeks of treatment with 40 mg after up-titration.

During an extended open-label treatment in 9 of these patients with 20 mg rosuvastatin for up to 90 weeks, the LDL-C reduction was maintained in the range of -12.1% to -21.3%.

In the 7 evaluable children and adolescent patients (aged from 8 to 17 years) from the force-titration open label study with homozygous familial hypercholesterolaemia (see above), the percent reduction in LDL-C (21.0%), Total-C (19.2%) and non-HDL-C (21.0%) from baseline following 6 weeks of treatment with rosuvastatin 20 mg was consistent with that observed in the aforementioned study in children and adolescents with homozygous familial hypercholesterolaemia.

The European Medicines Agency has waived the obligation to submit the results of studies with rosuvastatin in all subsets of the paediatric population in the treatment of homozygous familial hypercholesterolaemia, primary combined (mixed) dyslipidaemia and in the prevention of cardiovascular events.

Aspirin

Pharmacotherapeutic group: Platelet Aggregation Inhibitor Excl. Heparin, *ATC code*: B01AC06

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largely pre-systemic, associated with acetylation of platelet cyclo-oxygenase in the portal circulation.

Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclo-oxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of platelet aggregation. It also inhibits the action of cyclo-oxygenase in the vascular endothelial wall preventing the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.

However, as the endothelial cell is capable of synthesising new cyclo-oxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting.

Due to the low dose of Aspirin, acetylsalicylic acid is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. It is postulated that platelets passing through the portal circulation are exposed to acetylsalicylic acid concentrations sufficient to achieve effective thromboxane inhibition, while systemic prostacyclin synthesis remains essentially unaffected.

Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one reported study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *ex-vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.3 Pharmacokinetic properties

Rosuvastatin

Absorption: Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration. The absolute bioavailability is approximately 20%.

Distribution: Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90% of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism: Rosuvastatin undergoes limited metabolism (approximately 10%). Reported *In vitro* metabolism studies using human hepatocytes indicate that rosuvastatin is a poor substrate for cytochrome P450-based metabolism. CYP2C9 was the principal isoenzyme involved, with 2C19, 3A4 and 2D6 involved to a lesser extent. The main metabolites identified are the N-desmethyl and lactone metabolites. The N-desmethyl metabolite is approximately 50% less active than rosuvastatin whereas the lactone form is considered clinically inactive. Rosuvastatin accounts for greater than 90% of the circulating HMG-CoA reductase inhibitor activity.

Excretion: Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5% is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7%). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity: Systemic exposure of rosuvastatin increases in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Age and sex: There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to or lower than that in adult patients with dyslipidaemia (see "Paediatric population" below).

Race: Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and Cmax. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency: In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers. Steady-state plasma concentrations of rosuvastatin in subjects undergoing haemodialysis were approximately 50% greater compared to healthy volunteers.

Hepatic insufficiency: In a reported study with subjects with varying degrees of hepatic impairment, there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

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 a 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.

Paediatric population: Two pharmacokinetic studies with rosuvastatin (given as Capsules) in paediatric patients with heterozygous familial hypercholesterolaemia 10 to 17 or 6 to 17 years of age (total of 214 patients) demonstrated that exposure in paediatric patients appears comparable to or lower than that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

Pharmacokinetic properties

<u>Aspirin</u>

Aspirin is rapidly absorbed after oral administration of conventional release preparations, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks.

Absorption is more rapid in patients with achlorhydria and also following administration of polysorbates and antacids. Plasma concentrations of the drug increase disproportionately to the dose; e.g. a 325 mg dose having a half-life of 2-3 hours and higher doses showing lower plasma concentrations in the presence of an increased half-life due to a disproportionate increase in the volume of distribution.

Aspirin is found in saliva, milk, plasma and synovial fluid at concentrations less than in blood and crosses the placenta. Salicylate/protein binding extensive. Aspirin/protein binding to a small extent. In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate.

The absolute bioavailability of aspirin from Aspirin 75mg Gastro-Resistant Capsules (compared with intravenous aspirin solution) is approximately 25%.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Rosuvastatin

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in reported clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

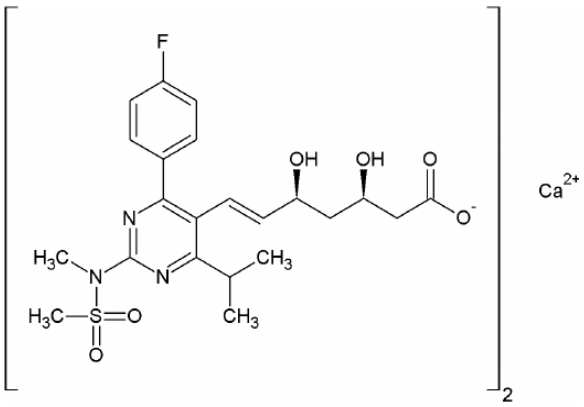
Aspirin

The nonclinical safety profile of acetylsalicylic acid is well documented.

In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications. Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

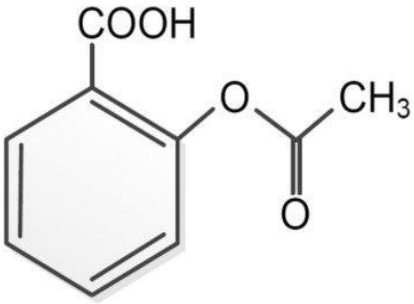
7. Description

Rosuvastatin Calcium is (E)-(3R,5S)-7-{4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulphonyamino)]pyrimidin-5- yl}-3,5-dihydroxyhepten-6-oic acid calcium having molecular formula of $(C_{22}H_{27}FN_3O_6S)_2$. Ca and molecular weight of is 1001.1. The Chemical structure is:



Rosuvastatin Calcium is an off-white to creamish white powder which is freely soluble in acetonitrile, and soluble in acetone.

Aspirin is 2-acetoxybenzoic acid having molecular formula $C_9H_8O_4$ and molecular weight of is 180.2. The Chemical structure is:



Aspirin is Colourless crystal or a white, crystalline powder, odourless or almost odourless.

ROZUCOR ASP-10 Size '0', hard gelatin capsules with Grey cap and White body containing one pink coloured, capsule shaped biconvex film coated tablets plain on both sides and one yellow coloured, round biconvex enteric-coated tablet plain on both sides.

ROZUCOR ASP- 20

Size '0', hard gelatin capsules with pink cap and yellow body containing one yellow coloured film coated tablet plain on both sides and one yellow coloured enteric-coated tablet, plain on both sides.

ROZUCOR ASP- 20/150

Size '0', hard gelatin capsules with blue cap and orange body containing one yellow coloured film coated tablet plain on both sides and two yellow colored enteric-coated tablet, plain on both sides.

The excipients used are Lactose Monohydrate, Microcrystalline Cellulose, Crospovidone, Magnesium Stearate, Lactose, Hydroxy propyl methyl Cellulose, Triacetin, Titanium dioxide, Ferric oxide red, Stearic acid, Ethyl Cellulose, Diethyl Phthalate, Iso Propyl

alcohol, Methlene Chloride, Talc, Triethyl Citrate, Ferric Oxide Yellow, Methacrylic Acid-Ethyl Acrylate Copolymer.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of Expiry

8.3 Packaging information

ROZUCOR ASP-10, 20 and 20/150 Available in strip pack of 10 capsules

8.4 Storage and handing instructions

Store at a temperature not exceeding 25°C, protected from light and moisture.

Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: information for the patient

ROZUCOR ASP

Rosuvastatin and Aspirin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What Rozucor Asp is and what it is used for

Rozucor Asp is a combination of Rosuvastatin (belongs to a group of medicines called statins) and Aspirin (belongs to a group of medicines called anti-platelet agents).

Aspirin, which in low doses belong to a group of medicines called anti-platelet agents. Platelets are tiny cells in the blood that cause the blood to clot and are involved in thrombosis. When a blood clot occurs in an artery it stops the blood flowing and cuts off

the oxygen supply. When this happens in the heart it can cause a heart attack or angina; in the brain it can cause a stroke.

You have a high cholesterol level. This means you are at risk from a heart attack or stroke. Rozucor Asp is used in adults, adolescents and children 6 years or older to treat high cholesterol.

You have been advised to take a statin, because changing your diet and doing more exercise were not enough to correct your cholesterol levels. You should continue with your cholesterol-lowering diet and exercise while you are taking Rozucor Asp.

Or

You have other factors that increase your risk of having a heart attack, stroke or related health problems. Heart attack, stroke and other problems can be caused by a disease called atherosclerosis. Atherosclerosis is due to build-up of fatty deposits in your arteries.

Why it is important to keep taking Rozucor Asp

Rozucor Asp is used to correct the levels of fatty substances in the blood called lipids, the most common of which is cholesterol.

There are different types of cholesterol found in the blood – 'bad' cholesterol (LDL-C) and 'good' cholesterol (HDL-C).

• **Rozucor Asp** can reduce the 'bad' cholesterol and increase the 'good' cholesterol.

• It works by helping to block your body's production of 'bad' cholesterol. It also improves your body's ability to remove it from your blood.

For most people, high cholesterol does not affect the way they feel because it does not produce any symptoms. However, if it is left untreated, fatty deposits can build up in the walls of your blood vessels causing them to narrow.

Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering your cholesterol levels, you can reduce your risk of having a heart attack, a stroke or related health problems.

You need to keep taking Rozucor Asp, even if it has got your cholesterol to the right level, because it prevents your cholesterol levels from creeping up again and causing build-up of fatty deposits. However, you should stop if your doctor tells you to do so, or you have become pregnant.

9.2 What you need to know before you take Rozucor Asp

Do not take Rozucor Asp:

• If you have ever had an allergic reaction to Rozucor Asp, other salicylates or non-steroidal anti-inflammatory drugs (NSAIDs) or to any of its ingredients.

• If you are pregnant or breast-feeding. If you become pregnant while taking Rozucor Asp stop taking it immediately and tell your doctor. Women should avoid becoming pregnant while taking Rozucor Asp by using suitable contraception.

• If you have liver disease.

• If you have severe kidney problems.

• If you have repeated or unexplained muscle aches or pains.

• If you take a drug called ciclosporin (used, for example, after organ transplants).

• have had an asthma attack or swelling of some parts of the body e.g. face, lips, throat or tongue (angioedema) after taking salicylates or NSAIDs

• Currently have or have ever had an ulcer in your stomach or small intestine or any other type of bleeding like a stroke

• have ever had the problem of your blood not clotting properly

• have severe liver or kidney problems

• suffer from gout

• Are in your last 3 months of pregnancy; you must not use higher doses than 100mg per day (see section "Pregnancy and breast-feeding")

• are taking a medicine called methotrexate (e.g. for cancer or rheumatoid arthritis) in doses higher than 15mg per week.

If any of the above applies to you (or you are in doubt), **please go back and see your doctor**.

Warnings and precautions

Talk to your doctor before taking Rozucor Asp.

• If you have problems with your kidneys.

• If you have problems with your liver.

• If you have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Tell your doctor immediately if you have unexplained muscle aches or pains, especially if you feel unwell or have a fever. Also, tell your doctor or pharmacist if you have a muscle weakness that is constant.

• If you regularly drink large amounts of alcohol.

• If your thyroid gland is not working properly.

• If you take other medicines called fibrates to lower your cholesterol. Please read this leaflet carefully, even if you have taken other medicines for high cholesterol before.

• If you take medicines used to treat the HIV infection e.g. ritonavir with lopinavir and/or atazanavir, please see "Other medicines and Rozucor Asp".

• If you are taking or have taken in the last 7 days a medicine called fusidic acid (a medicine for bacterial infection), orally or by injection. The combination of fusidic acid and Rozucor Asp can lead to serious muscle problems (rhabdomyolysis), please see "Other medicines and Rozucor Asp".

• If you are over 70 (as your doctor needs to choose the right start dose of Rozucor Asp to suit you)

• If you have severe respiratory failure.

• If you have ever had gout

- If you Are asthmatic, have hay fever, nasal polyps or other chronic respiratory diseases; acetylsalicylic acid may induce an asthma attack

• If you have heavy menstrual periods.

• If you are of Asian origin – that is Japanese, Chinese, Filipino, Vietnamese, Korean and Indian. Your doctor needs to choose the right start dose of Rozucor Asp to suit you.

If any of the above applies to you (or if you are not sure):

In a small number of people, statins can affect the liver. This is identified by a simple test which looks for increased levels of liver enzymes in the blood. For this reason, your doctor will usually carry out this blood test (liver function test) before and during treatment with Rozucor Asp.

While you are on this medicine your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. You are likely to be at risk of developing diabetes if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure.

You must immediately seek medical advice, if your symptoms get worse or if you experience severe or unexpected side effects e.g. unusual bleeding symptoms, serious skin reactions or any other sign of serious allergy (see section "Possible side effects").

Inform your doctor if you are planning to have an operation (even a minor one, such as tooth extraction) since acetylsalicylic acid is blood-thinning there may be an increased risk of bleeding.

You should take care not to become dehydrated (you may feel thirsty with a dry mouth) since the use of acetylsalicylic acid at the same time may result in deterioration of kidney function. This medicinal product is not suitable as a pain killer or fever reducer.

If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist.

Children and adolescents

• **If the patient is under 6 years old:** Rozucor Asp should not be given to children younger than 6 years.

• **If the patient is below 18 years of age:** The Rozucor Asp 40 mg Capsules is not suitable for use in children and adolescents below 18 years of age.

Ruzocor ASP contains Acetylsalicylic acid, it may cause Reye's syndrome when given to children. Reye's syndrome is a very rare disease which affects the brain and liver and can be life threatening. For this reason, Aspirin Tablets should not be given to children aged under 16 years, unless on the advice of a doctor

Other medicines and ROZUCOR ASP

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

Tell your doctor if you are taking any of the following:

- ciclosporin (used for example, after organ transplants),
- warfarin (or any other drug used for thinning the blood),
- fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe),
- indigestion remedies (used to neutralize acid in your stomach),
- erythromycin (an antibiotic), fusidic acid (an antibiotic – please see below and Warnings and precautions),

- an oral contraceptive (the pill),
- regorafenib (used to treat cancer),
- hormone replacement therapy
- Any of the following drugs used to treat viral infections, including HIV or hepatitis C infection, alone or in combination (please see Warnings and precautions): ritonavir, lopinavir, atazanavir, ombitasvir, paritaprevir, dasabuvir, velpatasvir, grazoprevir, elbasvir, glecaprevir, pibrentasvir.
- Mifepristone
- high blood pressure (e.g. diuretics and ACE-inhibitors)
- regulation of the heart beat (digoxin)
- manic-depressive illness (lithium)
- pain and inflammation (e.g. NSAIDs such as ibuprofen or steroids)
- gout (e.g. probenecid)
- glaucoma (acetazolamide)
- cancer or rheumatoid arthritis (methotrexate; in doses lower than 15mg per week)
- diabetes (e.g. glibenclamide)
- depression (selective serotonin re-uptake inhibitors (SSRIs) such as sertraline or paroxetine)
- use as hormone replacement therapy when the adrenal glands or pituitary gland have been destroyed or removed, or to treat inflammation, including rheumatic diseases and inflammation of the intestines (corticosteroids)
- Antacids (indigestion medicine).

The effects of these medicines could be changed by Rozucor ASP or they could change the effect of Rozucor ASP.

If you need to take oral fusidic acid to treat a bacterial infection you will need to temporarily stop using this medicine. Your doctor will tell you when it is safe to restart ROZUCOR ASP. Taking Rozucor ASP with fusidic acid may rarely lead to muscle weakness, tenderness or pain (rhabdomyolysis). See more information regarding rhabdomyolysis in.

Rozucor ASP Tablets with alcohol

Drinking alcohol may possibly increase the risk of gastrointestinal bleeding and prolong bleeding time.

Pregnancy and breast-feeding

Do not take Rozucor ASP if you are pregnant or breast-feeding. If you become pregnant while taking Rozucor ASP **stop taking it immediately** and tell your doctor. Women should avoid becoming pregnant while taking Rozucor ASP by using suitable contraception. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Most people can drive a car and operate machinery while using Rozucor ASP– it will not affect their ability. However, some people feel dizzy during treatment with Rozucor ASP. If you feel dizzy, consult your doctor before attempting to drive or use machines.

9.3 **How to take Rozucor ASP**

Always take this medicine as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Dose: As directed by Physician

If you take more Rozucor ASP than you should

Contact your doctor or nearest hospital for advice.

If you go into hospital or receive treatment for another condition, tell the medical staff that you're taking Rozucor ASP.

If you forget to take Rozucor ASP

Don't worry, just take your next scheduled dose at the correct time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Rozucor ASP

Talk to your doctor if you want to stop taking Rozucor ASP. Your cholesterol levels might increase again if you stop taking Rozucor ASP.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

It is important that you are aware of what these side effects may be. They are usually mild and disappear after a short time.

Stop taking Rozucor ASP and seek medical help immediately if you have any of the following allergic reactions:

• Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat.

• Swelling of the face, lips, tongue and/or throat, which may cause difficulty in swallowing.

• Severe itching of the skin (with raised lumps).

• Reddening of the skin with blisters or peeling and may be associated with a high fever and joint pains. This could by erythema multiforme, Stevens-Johnson syndrome or Lyell's syndrome.

• Unusual bleeding, such as coughing up blood, blood in your vomit or urine, or black stools.

Also, stop taking Rozucor ASP and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than you might expect. Muscle symptoms are more common in children and adolescents than in adults. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as *rhabdomyolysis*.

- If you experience muscle rupture.

- **If you have lupus-like disease syndrome** (including rash, joint disorders and effects on blood cells).

Common possible side effects (these may affect between 1 in 10 and 1 in 100 patients):

• Headache, stomach pain, constipation, feeling sick, muscle pain, feeling weak, dizziness.

• An increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking your ROZUCOR ASP Capsules (only ROZUCOR ASP40 mg).

• Diabetes. This is more likely if you have high levels of sugars and fats in your blood, are overweight and have high blood pressure. Your doctor will monitor you while you are taking this medicine.

• Indigestion.

• Increased tendency for bleeding.

Uncommon possible side effects (these may affect between 1 in 100 and 1 in 1,000 patients):

• Rash, itching or other skin reactions.

• An increase in the amount of protein in the urine - this usually returns to normal on its own without having to stop taking your ROZUCOR ASP Capsules (only ROZUCOR ASP5 mg, 10 mg and 20 mg).

• Hives.

• Runny noses.

• Breathing difficulty

Rare possible side effects (these may affect between 1 in 1,000 and 1 in 10,000 patients):

• Severe allergic reaction – signs include swelling of the face, lips, tongue and/or throat, difficulty in swallowing and breathing, a severe itching of the skin (with raised lumps).

If you think you are having an allergic reaction, then stop taking ROZUCOR ASP and seek medical help immediately.

• Muscle damage in adults – as a precaution, **stop taking ROZUCOR ASP and talk to your doctor immediately if you have any unusual aches or pains** in your muscles which go on for longer than expected.

• A severe stomach pain (inflamed pancreas).

• Increase in liver enzymes in the blood.

• Bleeding or bruising more easily than normal due to low level of blood platelets.

Vertigo, enlarged breasts in males. Nausea and vomiting.

• Lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

• Nausea and vomiting.

• Cramps in the lower respiratory tract, asthma attack.

• Inflammation in the blood vessels.

• Severe skin reactions such as rash known as erythema multiforme and it's life threatening forms Stevens-Johnson syndrome and Lyell's syndrome.

• Hypersensitivity reactions, such as swelling of e.g. lips, face or body, or shock.

• Abnormal heavy or prolonged menstrual periods.

Very rare possible side effects (these may affect less than 1 in 10,000 patients):

• Jaundice (yellowing of the skin and eyes), hepatitis (an inflamed liver), traces of blood in your urine, damage to the nerves of your legs and arms (such as numbness), joint pain, memory loss and breast enlargement in men (gynecomastia).

Side effects of unknown frequency may include:

• Diarrhoea (loose stools), Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals), cough, shortness of breath, oedema (swelling), sleep disturbances, including insomnia and nightmares, sexual difficulties, depression, breathing problems, including persistent cough and/or shortness of breath or fever, tendon injury and muscle weakness that is constant. Ringing in your ears (tinnitus) or reduced hearing ability. Head ache,

Vertigo, Ulcers in stomach or small intestine and perforation, Prolonged bleeding time, Impaired kidney function, Salt or water retention which may cause swelling of hands, feet, legs, stomach, breasts or face, Impaired liver function, High level of uric acid in the blood.

9.5 How to store ROZUCOR ASP

Store at a temperature not exceeding 25°C, protected from light and moisture. Keep out of reach of children.

9.6 Contents of the pack and other information

What ROZUCOR ASP contains:

The active substance in ROZUCOR ASP is Rosuvastatin and Aspirin. Contains Rosuvastatin calcium equivalent to 10 mg, 20 mg of Rosuvastatin and Aspirin 75mg and 150 mg:

The other ingredients are:

ROZUCOR ASP-10

Colour: Yellow Oxide of Iron Approved colours used in hard gelatin capsule shells.

ROZUCOR ASP-20

Colours: Red Oxide of Iron and Titanium Dioxide I.P.

Colour: Yellow Oxide of Iron

Approved colours used in hard gelatin capsule shells.

ROZUCOR ASP-20/150

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

Colour: Yellow Oxide of Iron

Approved colours used in hard gelatin capsule shells.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine

10. Details of manufacturer

Torrent Pharmaceutical LTD.

Indrad-382 721, Dist. Mehsana, INDIA.

At: Plot No: 26A-30, Sector-8A, IIE, SIDCUL,

Ranipur, Haridwar(Uttarakhand)-249 403.

11. Details of permission or licence number with date

24/UA/LL/2015 dated 10.08.2015

ROZUCOR ASP-20/150

24/UA/LL/2015 dated 22.09.2016

12. Date of revision

Feb-2021

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ROZUCOR ASP 10/75, 20/75, 20/150 Feb-21/02/PI