APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CREVAS 5 mg (5 mg film coated tablets)

CREVAS 10 mg (10 mg film coated tablets)

CREVAS 15 mg (15 mg film coated tablets)

CREVAS 20 mg (20 mg film coated tablets)

CREVAS 30 mg (30 mg film coated tablets)

CREVAS 40 mg (40 mg film coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CREVAS 5 mg: Each film coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).

CREVAS 10 mg: Each film coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).

CREVAS 15 mg: Each film coated tablet contains 15 mg rosuvastatin (as rosuvastatin calcium).

CREVAS 20 mg: Each film coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).

CREVAS 30 mg: Each film coated tablet contains 30 mg rosuvastatin (as rosuvastatin calcium).

CREVAS 40 mg: Each film coated tablet contains 40 mg rosuvastatin (as rosuvastatin

calcium).

Excipients with known effect

Each 5 mg film coated tablet contains sugar (lactose monohydrate 45,72 mg).

Each 10 mg film coated tablet contains sugar (lactose monohydrate 90,90 mg).

Each 15 mg film coated tablet contains sugar (lactose monohydrate 137,16 mg).

Each 20 mg film coated tablet contains sugar (lactose monohydrate 181,80 mg).

Each 30 mg film coated tablet contains sugar (lactose monohydrate 274,32 mg).

Each 40 mg film coated tablet contains sugar (lactose monohydrate 233,01 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated-tablets.

CREVAS 5 mg: Round, biconvex, yellowish film coated tablets, 6 mm in diameter, debossed with "5" on one side.

CREVAS 10 mg: Round, biconvex, light pink film coated tablets, 7 mm in diameter, debossed with "10" on one side.

CREVAS 15 mg: Round, biconvex, yellow film coated tablets, 8 mm in diameter, debossed with "15" on one side and "15" on the other side.

CREVAS 20 mg: Round, biconvex, dark pink film coated tablets, 9 mm in diameter, debossed with "20" on one side.

CREVAS 30 mg: Round, biconvex, yellow film coated tablets, 10 mm in diameter, debossed with "30" on one side.

CREVAS 40 mg: Round, biconvex, red film coated tablets, 10 mm in diameter, debossed

with "40" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk 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 high-sensitivity C-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CREVAS is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia

CREVAS is indicated for patients with primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia (including Fredrickson Type IIa, IIb and IV; and heterozygous familial and non-familial hypercholesterolaemia) as an adjunct to diet when response to diet and exercise is inadequate.

CREVAS is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia).

CREVAS is also indicated to reduce total cholesterol and LDL-C in patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

CREVAS 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of

CREVAS or alternative therapy and in whom routine follow-up will be performed.

Specialist supervision is recommended when the 40 mg dose is initiated (see section 4.4).

Children and adolescents 10 to 17 years of age

CREVAS is indicated to reduce the total cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

4.2 Posology and method of administration

Before treatment initiation the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment.

Posology

The dosage range for CREVAS is 5 - 40 mg orally once a day. The recommended starting dose is 5 mg once a day.

The choice of start dose should take into account the individual patient's cholesterol level and future cardiovascular risk as well as the potential risk for adverse reactions (see below). A dose adjustment to the next dose level can be made after 4 weeks, if necessary. In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to lower doses (see section 4.8), a final titration to the maximum dose of 40 mg should only be considered in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia), who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed (see section 4.4). Specialist supervision is recommended when the 40 mg dose is initiated.

The dose should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 4 week intervals.

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Frederickson Type III hyperlipoproteinaemia), and isolated hypertriglyceridaemia

The recommended starting dose is 5 mg once a day.

A 5 mg starting dose is recommended for patients of Asian ancestry and for patients requiring a smaller reduction in LDL-C to achieve treatment target.

For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a starting dose of 20 mg may be considered.

Homozygous familial hypercholesterolaemia

For patients with homozygous familial hypercholesterolaemia a starting dose of 20 mg once a day is recommended.

Special populations:

Use in the elderly

The usual dose range applies.

Dosage in patients with renal insufficiency

The starting dose applies in patients with mild to moderate renal impairment.

The 40 mg dose is contraindicated in patients with moderate renal impairment.

The use of CREVAS in patients with severe renal impairment is contraindicated for all doses (see sections 4.3 and 5.2).

Dosage in patients with hepatic insufficiency

The usual starting dose applies in patients with mild to moderate hepatic impairment. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9 (see section 5.2). In these patients an assessment of renal function should be considered (see section 4.4). There is no experience in subjects with Child-Pugh scores above 9.

Patients with severe hepatic impairment should start therapy with CREVAS 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above 10 mg should be carefully considered (see section 5.2). CREVAS is contraindicated in patients with active liver disease (see section 4.3).

Ethnic differences:

A 5 mg starting dose of CREVAS should be considered for Asian patients. Increased plasma concentration of rosuvastatin is seen in Asian subjects (see sections 4.4 and 5.2). The increased systemic exposure should be taken into consideration when treating Asian patients whose hypercholesterolaemia is not adequately controlled at doses up to 20 mg daily.

The 40 mg dose is contraindicated in these patients.

Genotypes of SLCO1B1 (OATP1B1) c.521CC and ABCG2 (BCRP) c.421AA have been shown to be associated with an increase in rosuvastatin exposure (AUC) compared to SLCO1B1 c.521TT and ABCG2 c.421CC. For patients known to have the c.521CC or c.421AA genotype, a maximum once daily dose of 20 mg of CREVAS should not be exceeded (see section 4.4, 4.5 and 5.2).

Concomitant therapy

CREVAS has 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.

CREVAS can also be used in combination with ezetimibe or bile acid sequestrants (see section 4.5).

Rosuvastatin is a substrate of various transporter proteins (e.g. OATP1B1 and BCRP). The risk of myopathy (including rhabdomyolysis) is increased when CREVAS is administered concomitantly with certain medicines 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 (see section 4.4 & 4.5).

It is recommended that prescribers consult the relevant product information when considering administration of such products together with CREVAS. Whenever possible, alternative medicines should be considered, and if necessary, consider temporarily discontinuing CREVAS therapy. In situations where co-administration of these medicinal

products with CREVAS is unavoidable, the risk of concurrent treatment and CREVAS dosing adjustments should be carefully considered (see section 4.4).

Interactions requiring dose adjustments

Ciclosporin

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant rosuvastatin and ciclosporin. For the CREVAS dose range (10 - 40 mg) this combination is contraindicated (see section 4.3).

Gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in subjects taking concomitant rosuvastatin and gemfibrozil. Patients taking this combination should start with therapy CREVAS 5 mg once daily and should not exceed a dose of CREVAS 20 mg once daily (see section 4.5).

Paediatric population

Children and adolescents 10 - 17 years of age

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5 - 20 mg orally once daily. The dose should be approximately titrated to achieve treatment goal. Safety and efficacy of doses greater than 20 mg have not been studied in this population.

In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

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Method of Administration

For oral administration.

CREVAS may be given at any time of day, with or without food.

4.3 Contraindications

CREVAS is contraindicated

- in patients with hypersensitivity to rosuvastatin or to any of the excipients of CREVAS (see section 6.1)
- 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 receiving concomitant ciclosporin (see section 4.5)
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures (see section 4.6)
- in patients with myopathy
- The 40 mg dose is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
  - moderate renal impairment (creatinine clearance < 60 mL/min)
  - hypothyroidism
  - personal or family history of hereditary muscular disorders
  - previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
  - alcohol abuse

- situations where an increase in rosuvastatin-plasma levels may occur
- Asian patients
- concomitant use of fibrates (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

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 40 mg. This condition was transient or intermittent in most cases. Proteinuria has not been shown to be a precursor to acute or progressive renal disease (see section 4.8).

The reporting rate for serious renal events in post-marketing use is higher at the 40 mg dose. An assessment of renal function must be considered during routine follow-up of patients treated with a dose of 40 mg.

There have been rare post marketing reports of fatal and non-fatal hepatic failure in patients taking statins, including CREVAS. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment with CREVAS, promptly interrupt therapy. If an alternate aetiology is not found, do not restart CREVAS.

Skeletal Muscle Effects

Risk of myasthenia gravis and ocular myasthenia.

Effects on skeletal muscle e.g. myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients at all doses, particularly at doses higher than 20 mg.

As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose. Patients who develop any signs or symptoms suggestive of myopathy should have their Creatine Kinase (CK) levels measured. CREVAS therapy should be discontinued if myopathy is diagnosed or suspected.

An increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

CREVAS should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism, or situations where an increase in plasma levels may occur (see section 5.2).

Creatine Kinase Measurement

Creatine Kinase (CK) should not be measured following strenuous exercise or in the presence of alternative causes of CK increase which may influence the interpretation of the result. If CK levels are significantly elevated at baseline (> 5 x ULN) a confirmatory test should be carried out within 5 - 7 days. If the repeat test confirms a baseline CK > 5 x ULN, treatment must not be started.

Before treatment

HMG-CoA reductase inhibitors, such as CREVAS, should be prescribed with caution in patients with predisposing 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
- above 70 years of age
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)
- concomitant use of fibrates.

In this patient group, the risk of treatment should be considered in relation to possible benefit. Clinical monitoring is recommended. If CK levels are significantly elevated at baseline (> 5 x ULN) treatment must not be initiated.

During treatment

Patients must be advised 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 must be discontinued if CK levels are markedly elevated (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN).

If symptoms resolve and CK levels return to normal, then consideration should be given to reintroducing CREVAS 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 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.

Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive medicines may be required.

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.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with rosuvastatin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of this reaction appear, CREVAS should be discontinued immediately and an alternative treatment should be considered.

If the patient has developed a serious reaction such as SJS or DRESS with the use of CREVAS, treatment with CREVAS must not be restarted in this patient at any time.

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Gemfibrozil

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

The 40 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.5 and 4.8).

Fusidic acid

CREVAS 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 (see section 4.5).

Patients are to be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be reintroduced 7 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 concomitant administration of CREVAS and fusidic acid should only be considered on a case by case basis and under close medical supervision.

CREVAS must not be used in patients with acute, serious conditions 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

HMG-CoA reductase inhibitors, such as CREVAS, must 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. CREVAS must be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

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

Ethnic differences

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasian subjects (see sections 4.2, 4.3 and 5.2).

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 CREVAS in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating CREVAS doses in patients treated with protease inhibitors.

The concomitant use with certain protease inhibitors is not recommended unless the dose of CREVAS is adjusted (see sections 4.2 and 4.5).

Interstitial Lung Disease

Cases of interstitial lung disease have been reported with some statins, especially with long-term therapy (see section 4.8). Presenting features may 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 must be discontinued.

Diabetes Mellitus

Statins as a class of medicine may raise blood glucose. 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.

CREVAS should be used with care in patients with Type 2 diabetes and in patients at risk, being patients with a fasting glucose of 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides or hypertension. Patients at risk must be clinically and biochemically monitored.

Lactose Intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CREVAS.

Excipients

CREVAS 5 mg, 15 mg and 30 mg contains quinoline yellow aluminium lake (E104).

CREVAS 10 mg contains alura red aluminium lake (E129).

CREVAS 40 mg contains sunset yellow aluminium lake (E110) and ponceau aluminium lake (E124).

The above colourants may cause allergic reactions.

Children and adolescents 10 – 17 years of age

The safety profile of CREVAS is similar in children or adolescent patients and adults, although CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity, which resolved with continued treatment, were observed more frequently in children and adolescents. However, the same special warnings and special precautions for use in adults also apply to children and adolescents.

The evaluation of linear growth (height), weight, BMI (body mass index), and secondary characteristics of sexual maturation by Tanner staging in paediatric patients taking rosuvastatin is limited to a 1 year period.

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4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on CREVAS

Transporter protein inhibitors

Rosuvastatin, as contained in CREVAS, is a substrate for certain transporter proteins including the hepatic uptake transporter organic-anion-transporting polypeptide 1B1 (OATP1B1) and efflux transporter breast-cancer-resistance protein (BCRP). Concomitant administration of CREVAS with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5 Table 1).

Ciclosporin

During concomitant treatment with rosuvastatin and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). CREVAS is contraindicated in patients receiving concomitant ciclosporin (see section 4.3). Concomitant administration did not affect plasma concentrations of ciclosporin.

Protease inhibitors

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving rosuvastatin with various protease inhibitors in combination with ritonavir (see Table 1 below). This increase in systemic exposure to rosuvastatin may lead to an increased incidence of adverse events.

The concomitant use of CREVAS and some protease inhibitor combinations may be considered after careful consideration of CREVAS dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.4 and Table 1 below).

Gemfibrozil and other lipid-lowering medicines

Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).

No pharmacokinetic relevant interaction with fenofibrate has been reported, 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 such as rosuvastatin contained in CREVAS, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate (see sections 4.3 and 4.4). These patients should start with the 5 mg dose.

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 (Table 1). A pharmacodynamic interaction, in terms of adverse effects, between CREVAS and ezetimibe cannot be ruled out (see section 4.4).

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 CREVAS. The clinical relevance of this interaction has not been studied.

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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.

Ticagrelor

Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis.

Cytochrome P450 enzymes

In vitro and *in vivo* data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer). Therefore, medicine 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 (see also Table 1 below)

When it is necessary to co-administer CREVAS with other medicines known to increase exposure to rosuvastatin, doses of CREVAS should be adjusted.

Start with a 5 mg once daily dose of CREVAS if the expected increase in exposure (AUC) is approximately 2-fold or higher.

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The maximum daily dose of CREVAS should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of CREVAS taken without interacting medicines, for example a 20 mg dose of CREVAS with gemfibrozil (1,9-fold increase), and a 10 mg dose of CREVAS with combination ritonavir/atazanavir (3,1-fold increase).

If medicine 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 CREVAS dose above 20 mg.

Table 1 Effect of co-administered medicines 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 medicine 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	10 mg single dose	7,4-fold ↑
Ciclosporin 75 mg twice daily to 200 mg	10 mg once daily, 10 days	7,1-fold ↑

twice daily, 6 months		
Darolutamide 600 mg, twice daily, 5 days	5 mg, single dose	5,2-fold ↑
Regorafenib 160 mg, once daily, 14 days	5 mg, single dose	3,8-fold ↑
Atazanavir 300 mg/ritonavir 100 mg once daily, 8 days	10 mg, single dose	3,1-fold ↑
Simeprevir 150 mg one daily, 7 days	10 mg, single dose	2,8-fold ↑
Velpatasvir 100 mg once daily	10 mg, single dose	2,7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg once daily / dasabuvir 400 mg twice daily, 14 days	5 mg, single dose	2,6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg once daily, 11 days	10 mg, single dose	2,3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg once daily, 7 days	5 mg once daily, 7 days	2,2-fold ↑

Lopinavir 400 mg/ritonavir 100 mg twice daily, 17 days	20 mg once daily, 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 twice daily, 7 days	80 mg, single dose	1,9-fold ↑
Less than 2-fold increase in AUC of rosuvastatin		
Eltrombopag 75 mg once daily, 5 days	10 mg, single dose	1,6-fold ↑
Darunavir 600 mg/ritonavir 100 mg twice daily, 7 days	10 mg once daily, 7 days	1,5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg twice daily, 11 days	10 mg, single dose	1,4-fold ↑
Dronedarone 400 mg twice daily	Not available	1,4-fold ↑
Itraconazole 200 mg once daily, 5 days	10 mg, single dose	**1,4-fold ↑
Ezetimibe 10 mg once daily, 14 days	10 mg, once daily, 14 days	**1,2-fold ↑
No clinically significant effect on the AUC ratio		

Fosamprenavir 700 mg/ritonavir 100 mg twice daily, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg three times daily, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg three times daily, 7 days	10 mg, 7 days	↔
Rifampicin 450 mg once daily, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg twice daily, 7 days	80 mg, single dose	↔
Fluconazole 200 mg once daily, 11 days	80 mg, single dose	↔
Decrease in AUC of rosuvastatin		
Erythromycin 500 mg four times daily, 7 days	80 mg, single dose	20 % ↓
Baicalin 50 mg three times daily, 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 "↔", decrease as "↓".

** Several interaction studies have been performed at different dosages, the table shows the most significant ratio.

Effect of rosuvastatin on co-administered medicines

Warfarin

The pharmacokinetics of warfarin are not significantly affected following co-administration with CREVAS. However, co-administration of CREVAS and warfarin may result in a rise in International Normalised Ratio (INR) compared to warfarin alone. In patients taking warfarin, monitoring of INR is recommended both at initiation or cessation of therapy with CREVAS or following dose adjustment.

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 CREVAS and hormone replacement therapy, therefore, a similar effect cannot be excluded.

Niacin

CREVAS, when used in combination with lipid-modifying doses (≥ 1 g/day) of niacin, may enhance the risk of skeletal muscle effects caution should therefore be used when prescribing with CREVAS (see section 4.4).

Consideration should be given both to the benefit of lipid lowering by the use of CREVAS in HIV-infected patients receiving protease inhibitors and the potential risks of this increased rosuvastatin plasma concentrations when initiating and up-titrating CREVAS doses in patients treated with protease inhibitors, as the combination may lead to an increased incidence of adverse events (see sections 4.2 and 4.4).

The lowest dose of CREVAS that provides therapeutic benefit to the patient should be used and close monitoring of adverse events is indicated (see section 4.2).

Other medicines

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, CREVAS treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Study data with rosuvastatin co-administered with antihypertensive agents and antidiabetic agents did not produce any evidence of clinically significant adverse interactions.

Paediatric population:

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

CREVAS is contraindicated in pregnancy (see section 4.3).

Breastfeeding

CREVAS is contraindicated in lactation. Rosuvastatin is excreted in the milk of rats. There is no data available with respect to excretion of rosuvastatin in milk in humans (see section 4.3).

Fertility

No data is available on fertility.

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4.7 Effects on ability to drive and use machines

Studies to determine the effect of CREVAS on the ability to drive and use machines have not been conducted. However, based on its pharmacodynamic properties, CREVAS is unlikely to affect this ability.

CREVAS may cause dizziness, therefore patients taking CREVAS should not drive or use machines until their individual susceptibility to dizziness is known.

4.8 Undesirable effects

Summary of the safety profile

The adverse reactions seen with CREVAS are generally mild and transient.

The incidence of adverse reactions tends to increase with increasing dose.

Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions including angioedema
Endocrine disorders	Frequent	Diabetes mellitus[1]
Psychiatric disorders	Frequency unknown	Depression

Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Polyneuropathy, memory loss
	Frequency unknown	Peripheral neuropathy, sleep disturbance (including insomnia and nightmares) Myasthenia gravis
Eye disorders	Frequency unknown	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough, dyspnoea
Gastro-intestinal disorders	Frequent	Constipation, nausea, abdominal pain
	Less frequent	Pancreatitis
	Frequency unknown	Diarrhoea
Hepatobiliary disorders	Less frequent	Increased hepatic transaminases, jaundice, hepatitis
	Frequency unknown	Fatal and non-fatal hepatic failure
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, urticaria
	Frequency unknown	Stevens- Johnson syndrome, Drug reaction with eosinophilia and

		systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Frequent	Myalgia
	Less frequent	Myopathy (including myositis), rhabdomyolysis, Lupus-like syndrome, muscle rupture, arthralgia
	Frequency unknown	Tendon disorders, sometimes complicated by rupture, immune-mediated necrotising myopathy
Renal and urinary disorders	Less frequent	Haematuria
	Frequency unknown	Proteinuria
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Asthenia
	Less frequent	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, such as CREVAS, the incidence of adverse reactions tends to be dose dependent.

There have been post-marketing reports of cognitive impairment (e.g. memory loss,

forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive 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 of 3 weeks).

Description of selected adverse reactions

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with CREVAS. Shifts in urine protein from none or trace to 100 mg/dL 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 30 mg/dL 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 CREVAS 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 CREVAS-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 (> 5 x ULN), treatment should be discontinued (see section 4.4).

Liver effects

A dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin as in CREVAS; 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 (see section 4.4)
- 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.

Other effects

In a long-term controlled clinical trial rosuvastatin was shown to have no harmful effects on the ocular lens.

In rosuvastatin treated patients, there was no impairment of adrenocortical function.

The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest marketed dose.

Paediatric population

Children and adolescents 10 – 17 years of age

Creatine kinase elevations > 10 x ULN 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 (see section 4.4).

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company,

pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 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.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10AA07

Pharmacological classification: A 7.5 Serum-cholesterol reducers

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-CoA (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 produces its lipid-modifying effects in 2 ways; it increases the number of hepatic low density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very low density lipoprotein (VLDL**)**, thereby reducing the total number of VLDL and LDL particles.

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

Rosuvastatin reduces elevated LDL-cholesterol (LDL-C), total cholesterol and triglycerides (TG) and increases HDL-cholesterol (HDL-C). It also lowers apolipoprotein B (ApoB) non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I. 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 by 4 weeks and is maintained after that.

5.2 Pharmacokinetic properties

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. The parent compound accounts for greater than 90 % of the circulating active HMG-CoA reductase inhibitor activity.

Biotransformation:

Rosuvastatin undergoes limited metabolism in humans (approximately 10 %) mainly to the N-desmethyl form.

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.

Elimination:

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 the 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. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to or lower than that of adult

volunteers with dyslipidaemia (see Paediatric population below).

Ethnic differences

Pharmacokinetic studies show a 1,26 - 2,31-fold elevation in geometric mean AUC ($_{0\text{-}t}$) in Asian subjects compared with Caucasians.

A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) Philipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analyses in these studies.

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. (see section 4.2, Ethnic differences).

Renal insufficiency

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentration of rosuvastatin. However, subjects with severe impairment (Cr_{Cl} < 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 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 tablets) 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

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Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Opadry coating[1]

Hypromellose (E464)

Lactose monohydrate

Titanium dioxide (E171)

Triacetin (E1518)

Opadry II 31K38097 Yellow (5 mg, 15 mg and 30 mg)

Quinoline yellow aluminium lake (E104)

Opadry II 32K240042 Pink (10 mg):

Allura red aluminium lake (E129)

Opadry II 32K240039 Pink (20 mg):

Carmine (E120)

Opadry II 32K250001 (40 mg)

Ponceau aluminium lake (E124)

Sunset yellow aluminium lake (E110)

[1]Applicable to the coating of all strengths

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 30 °C in a cool, dry place. Protect from light. Keep the tablets in the outer carton until required for use.

6.5 Nature and contents of container

CREVAS is available in polyamide/aluminium/PVC/aluminium foil blister strips, packed in an outer carton, in packs of 7, 14, 28, 30, 56 or 98 film coated tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

Tel.: +27 21 707 7000

or 0860-PHARMA (742 762)

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8. REGISTRATION NUMBERS

CREVAS 5 mg: A46/7.5/0313

CREVAS 10 mg: A46/7.5/0314

CREVAS 15 mg: A55/7.5/0453*

CREVAS 20 mg: A46/7.5/0315

CREVAS 30 mg: A55/7.5/0454*

CREVAS 40 mg: A46/7.5/0316*

9. DATE OF FIRST AUTHORISATION

CREVAS 5 mg: 12 July 2022

CREVAS 10 mg: 12 July 2022

CREVAS 15 mg: 02 May 2023

CREVAS 20 mg: 12 July 2022

CREVAS 30 mg: 02 May 2023

CREVAS 40 mg: 12 July 2022

10. DATE OF REVISION OF THE TEXT

27 August 2025

NAMIBIA

CREVAS 5 mg: NAM NS2 21/7.5/0057

CREVAS 10 mg: NAM NS2 21/7.5/0058

CREVAS 20 mg: NAM NS2 21/7.5/0059

CREVAS 40 mg: NAM NS2 21/7.5/0060

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MOZAMBIQUE*

CREVAS 5 mg: C6912

CREVAS 10 mg: C6913

CREVAS 20 mg: C6914

*CREVAS 15 mg, CREVAS 30 mg and CREVAS 40 mg are not marketed in Mozambique.