PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

CRESAGEN 5 Tablets

CRESAGEN 10 Tablets

CRESAGEN 20 Tablets

CRESAGEN 40 Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CRESAGEN 5: Each film-coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium)

CRESAGEN 10: Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium)

CRESAGEN 20: Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium)

CRESAGEN 40: Each film-coated tablet contains 40 mg rosuvastatin (as rosuvastatin calcium)

Excipients with known effect

Each 5 mg film-coated tablet contains 45.72 mg lactose monohydrate.

Each 10 mg film-coated tablet contains 90.90 mg lactose monohydrate.

Each 20 mg film-coated tablet contains 181.80 mg lactose monohydrate.

Each 40 mg film-coated tablet contains 233.005 mg lactose monohydrate.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

CRESAGEN 5: Round, biconvex, yellow film-coated tablets, 6 mm in diameter, debossed with “5” on one side.

CRESAGEN 10: Round, biconvex, yellow film-coated tablets, 7 mm in diameter, debossed with “10” on one side.

CRESAGEN 20: Round, biconvex, yellow film-coated tablets, 9 mm in diameter, debossed with “20” on one side.

CRESAGEN 40: Round, biconvex, yellow film-coated tablets, 10 mm in diameter, debossed with “40” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adult patients with hypercholesterolaemia:

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

CRESAGEN is also indicated for patients with homozygous familial hypercholesterolaemia, either alone or as an adjunct to diet and other lipid lowering treatments (e.g. LDL apheresis).

CRESAGEN 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 **CRESAGEN** or alternative therapy.

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 **CRESAGEN** is 5 - 40 mg orally once a day. The recommended start dose is 5 mg once a day.

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 2 – 4 week intervals.

Adults:

Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia 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 of 5 mg applies in patients with mild to moderate renal impairment.

CRESAGEN is contraindicated in severe renal impairment (see section 4.3).

Dosage in patients with hepatic insufficiency:

The usual starting dose of 5 mg applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with **CRESAGEN** 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above **CRESAGEN** 10 mg should be carefully considered (see section 5.2).

Race:

A 5 mg starting dose of **CRESAGEN** 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.

Concomitant therapy:

CRESAGEN 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.

CRESAGEN can also be used in combination with ezetimibe or bile acid sequestrants (see section 4.4).

Interactions requiring dose adjustments:

Ciclosporin:

CRESAGEN is contraindicated in patients receiving ciclosporin (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 therapy with **CRESAGEN** 5 mg once daily and should not exceed a dose of **CRESAGEN** 20 mg once daily (see section 4.5).

Paediatric population

Children and adolescents 10 - 17 years of age:

Safety and efficacy has not been established in children. Paediatric experience is limited to a small number of children (aged 8 years and above) with homozygous familial hypercholesterolaemia.

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.

Method of administration

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

4.3 Contraindications

CRESAGEN is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients of **CRESAGEN**.
- 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, 4.5 and 5.2).

4.4 Special warnings and precautions for use

Risk of myasthenia gravis and ocular myasthenia

Renal Effects

An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40 mg.

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, it 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).

Skeletal Muscle Effects

Effects on skeletal muscle e.g. uncomplicated myalgia, myopathy and rhabdomyolysis have been reported in patients treated with **CRESAGEN**. The reporting rate for rhabdomyolysis in post-marketing use is higher at the highest dose. Patients who develop any signs or symptoms suggestive myopathy should have their creatine kinase (CK) levels measured. **CRESAGEN** therapy should be discontinued if myopathy is diagnosed or suspected.

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

CRESAGEN should be prescribed with caution in patients with pre-disposing factors for myopathy and rhabdomyolysis such as renal impairment, hypothyroidism, history of hereditary muscular disorders, history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate, alcohol abuse, age > 70 years, concomitant use of fibrates and situations where an increase in plasma levels may occur.

CRESAGEN should be temporarily withheld in any patient with an acute serious condition suggestive of myopathy or pre-disposing to the development of renal failure secondary to rhabdomyolysis (e.g. sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorder; or uncontrolled seizures).

Concomitant use with protease inhibitors in HIV patients.

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 **CRESAGEN**, 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
- 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 re-introducing **CRESAGEN** 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.

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

Increased systemic exposure to rosuvastatin has been reported in subjects taking concomitant **CRESAGEN** and gemfibrozil. Patients taking this combination should start therapy with **CRESAGEN** 5 mg once daily and should not exceed a dose of **CRESAGEN** 20 mg once daily (see sections 4.5 and 4.8).

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

Fusidic acid

CRESAGEN 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 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 concomitant administration of **CRESAGEN** and fusidic acid should only be considered on a case by case basis and under close medical supervision.

CRESAGEN 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

Liver enzyme tests should be performed in patients before initiating **CRESAGEN** therapy and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate aetiology is not found, **CRESAGEN** should not be restarted.

CRESAGEN should be used with caution in patients who consume substantial

quantities of alcohol and/or have a history of chronic liver disease. Active liver disease, which may include unexplained persistent transaminase elevations, is a contra-indication to the use of **CRESAGEN** (see section 4.2)

It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. **CRESAGEN** 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.

Race

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

CRESAGEN should be used with caution in patients taking various protease inhibitors in combination with ritonavir, as pharmacokinetic studies have shown an increase in the AUC and C_{max} of rosuvastatin (see sections 4.2 and 4.5).

Consideration should be given both to the benefit of lipid lowering by use of **CRESAGEN** in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating **CRESAGEN** doses in patients treated with protease inhibitors.

The concomitant use with certain protease inhibitors is not recommended unless the dose of **CRESAGEN** 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, **CRESAGEN** must be discontinued.

Diabetes Mellitus

Increases in glycosylated haemoglobin (HbA1c) fasting serum glucose levels and worsening of glycaemic control have been reported with the use of statins, such as **CRESAGEN**. **CRESAGEN** should therefore be used with care in patients with type 2 diabetes. This risk, however, is outweighed by the reduction in vascular risk with statins and therefore should not be a reason for stopping statin treatment.

CRESAGEN 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/m2, raised triglycerides or hypertension. Patients at risk must be clinically and biochemically monitored.

Although reported clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if **CRESAGEN** is administered concomitantly with agents that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone,and cimetidine.

Nervous system effects

There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with the use of statins such **CRESAGEN**. These reported symptoms were generally not serious and reversible upon discontinuation with variable times to symptom onset (between a day to years) and symptom resolution with a median of 3

weeks.

Lactose Intolerance

CRESAGEN contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on* CRESAGEN*:

Transporter protein inhibitors:

Rosuvastatin, as contained in **CRESAGEN**, 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 **CRESAGEN** 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: **CRESAGEN** is contraindicated in patients receiving ciclosporin (see section 4.3). Co-administration of rosuvastatin with ciclosporin resulted in no significant changes in ciclosporin plasma concentration. However, after co-administration with ciclosporin, rosuvastatin steady plasma concentration state $AUC_{(0-t)}$ increased up to 7- fold over that reported in healthy volunteers administered the same dose of rosuvastatin (see section 4.2).

Gemfibrozil: Concomitant use of **CRESAGEN** and gemfibrozil resulted in a 2-fold increasein rosuvastatin C_{max} and $AUC_{(0-t)}$.

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 **CRESAGEN**, 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.

Protease inhibitors: (See section 4.4)

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 **CRESAGEN** and some protease inhibitor combinations may be considered after careful consideration of **CRESAGEN** dose adjustments based on the expected increase in rosuvastatin exposure (see sections 4.2, 4.4, 4.5 and Table 1 below).

Antacids: 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 reported.

Cytochrome P450 enzymes: In vivo and *in vitro* data indicate that **CRESAGEN**, containing rosuvastatin, has no clinically significant cytochrome P450 interactions (as a substrate, inhibitor or inducer).

Niacin: The risk of skeletal muscle effects may be enhanced when **CRESAGEN** is used in combination with niacin; a reduction in **CRESAGEN** dosage should be considered in this setting.

Fenofibrate: When **CRESAGEN** was co-administered with fenofibrate no clinically significant increase in the AUC of rosuvastatin or fenofibrate was reported. The benefit of further alterations in lipid levels by the combined use of **CRESAGEN** with fibrates shouldbe carefully weighed against the potential risks of this combination.

Erythromycin: Concomitant use of rosuvastatin and erythromycin can result in a 20 % decrease in the $AUC_{(0-t)}$ and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gastro-intestinal motility caused by erythromycin.

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 **CRESAGEN** and ezetimibe cannot be ruled out (see section 4.4).

Other medications: In clinical studies rosuvastatin was co-administered with antihypertensive agents, anti-diabetic agents and hormone replacement therapy. These reported studies did not produce any evidence of clinically significant adverse reactions.

Interactions requiring rosuvastatin dose adjustments (see also Table 1 below):

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

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

The maximum daily dose of **CRESAGEN** should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of **CRESAGEN** taken without interacting medicines, 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).

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 BID to 200 mg BID, 6 months	10 mg OD, 10 days	7.1-fold ↑
Darolutamide 600 mg BID, 5 days	5 mg, 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 ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2,8-fold ↑

Velpatasvir 100 mg OD	10 mg, single dose	2.7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg / dasabuvir 400 mg BID	5 mg, single dose	2.6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD	10 mg, single dose	2.3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD for 7 days	5 mg once daily, 7 days	2.2-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 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 BID, 7 days	80 mg, single dose	1.9-fold ↑

Less than 2-fold increase in AUC of rosuvastatin

Interacting medicine 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 or 80 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

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 "↑", decrease as "↓".

** Several interaction studies have been performed at different 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 CRESAGEN on co-administered medicines:

Warfarin: The pharmacokinetics of warfarin is not significantly affected following co- administration with rosuvastatin. However, co-administration of **CRESAGEN** and warfarin may result in a rise in INR compared to warfarin alone. In patients taking warfarin monitoring of INR is recommended both at initiation or cessation of therapy with **CRESAGEN** or following dose adjustment.

Oral contraceptive/hormone replacement therapy (HRT): Concomitant use of rosuvastatin and an oral contraceptive can result in an increase in ethinyl oestradiol and norgestrel AUC of 26 % and 34 % respectively. These increased plasma levels should be considered when selecting oral contraceptive doses. Although there are no pharmacokinetic data available in women taking concomitant HRT, a similar effect cannot be excluded.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential /Contraception in males and females

Women of child-bearing potential should use appropriate contraceptive measures.

Pregnancy

CRESAGEN is contraindicated in pregnancy (see section 4.3).

Breastfeeding

CRESAGEN is contraindicated in lactation. (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions seen with **CRESAGEN** are generally mild and transient.

Table 2: Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions including angioedema
Endocrine disorders	Frequent	Diabetes Mellitus
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache, dizziness
	Less frequent	Cognitive impairment such as memory loss, forgetfulness, amnesia, memory impairment and confusion, polyneuropathy
	Frequency unknown	Peripheral neuropathy, sleep disturbances (including insomnia and nightmares), myasthenia

MedDRA system organ class	**Frequency**	**Adverse reactions**
		gravis
Eye disorders	Frequency unknown	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough dyspnoea
Gastrointestinal disorders	Frequent	Constipation, nausea, abdominal pain
	Less frequent	Pancreatitis
Hepato-biliary 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
Musculoskeletal and connective tissue disorders	Frequent	Myalgia
	Less frequent	Myopathy (including myositis) Rhabdomyolysis, which may occasionally be associated with impairment of renal function, arthralgia, Lupus-like syndrome, muscle rupture, athralgia

MedDRA system organ class	Frequency	Adverse reactions
	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

[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 rosuvastatin, the incidence of adverse 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 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 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 (> 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 **CRESAGEN**; 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.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

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 (see Section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A07

A 7.5 Serum-cholesterol reducers

Mechanism of action

Rosuvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Rosuvastatin produces its lipid-modifying effects in 2 ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and inhibits hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

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

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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.

Elimination

Approximately 90 % of the rosuvastatin dose is excreted unchanged in the faeces and the remaining part is excreted in the urine.

Linearity/non-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 that of adult volunteers.

Race:

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

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

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 (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

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.

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

crospovidone type A

lactose monohydrate

magnesium stearate

microcrystalline cellulose type 102.

Tablet coat: hypromellose (E464), lactose monohydrate, quinoline yellow

aluminium lake (E104),titanium dioxide (E171), triacetin (E1518).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Cartons contain 28 or 30 tablets packed into PA-Aluminium-PVC laminate and aluminium foil blister strips of 7 or 8 tablets each.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd Oval Business Park, Wanderers Building, Unit 1B,Office A, Cnr Sloane and Meadowbrook Close,

Bryanston 2194

8 REGISTRATION NUMBER(S)

CRESAGEN 5: 44/7.5/1065

CRESAGEN 10: 44/7.5/1066

CRESAGEN 20: 44/7.5/1067

CRESAGEN 40: 44/7.5/1068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

March 2014

10 DATE OF REVISION OF THE TEXT

28 November 2023