PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

XARTIGEN 5 (5 mg film-coated tablets)

XARTIGEN 10 (10 mg film-coated tablets)

XARTIGEN 20 (20 mg film-coated tablets)

XARTIGEN 40 (40 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

Excipients with known effect:

Contains sugar:

Each 5 mg film-coated tablet contains 92,20 mg lactose monohydrate.

Each 10 mg film-coated tablet contains 89,20 mg lactose monohydrate.

Each 20 mg film-coated tablet contains 178,40 mg lactose monohydrate.

Each 40 mg film-coated tablet contains 164,40 mg lactose monohydrate.

XARTIGEN 40: Contains Sunset yellow FCF aluminium lake.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

XARTIGEN 5: Yellow, round, biconvex, film-coated tablet, debossed “5” on one side and “R” on other side.

XARTIGEN 10: Pink, round, biconvex, film-coated tablet, debossed “10” on one side and “R” on other side.

XARTIGEN 20: Pink, round, biconvex, film-coated tablet, debossed “20” on one side and “R” on other side.

XARTIGEN 40: Pink, oval, biconvex, film-coated tablet, debossed “40” on one side and “R” on other 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-reaction protein (hsCRP) level, age, hypertension, low high-density lipoprotein cholesterol (HDL-C), smoking or a family history of premature coronary heart disease. **XARTIGEN** is indicated to reduce the risk of non-fatal stroke, non-fatal myocardial infarction (MI), and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

XARTIGEN 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.

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

XARTIGEN 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).

XARTIGEN 40 should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of **XARTIGEN** or alternative therapy.

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

Children and adolescents 10 to 17 years of age:

XARTIGEN is indicated to reduce the total cholesterol, LDL-C and Apo B scores, 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 dose range for **XARTIGEN** is 5 to 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 to 4-week intervals.

Adults

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

The recommended starting dose is 5 mg orally 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. For patients with severe renal impairment the dose of **XARTIGEN** should not exceed 10 mg once daily.

Dosage in patients with hepatic impairment

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

Race

A 5 mg starting dose of **XARTIGEN** 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

XARTIGEN 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.

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

Interactions requiring dose adjustments

Ciclosporin

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant **XARTIGEN** and ciclosporin. For the **XARTIGEN** dose range (10 mg to 40 mg) this combination is not

recommended (see section 4.3).

Gemfibrozil

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

Paediatric population

Children and adolescents 10 to 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 appropriately titrated to achieve the 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).

Method of administration

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

4.3. Contraindications

XARTIGEN is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients of **XARTIGEN**.
- 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

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of **XARTIGEN**, 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).

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.

Skeletal muscle effects

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. **XARTIGEN** 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.

XARTIGEN should be prescribed with caution in patients with pre-disposing 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 to 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 **XARTIGEN**, 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 reintroducing **XARTIGEN** 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

Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors, such as **XARTIGEN**. Therefore, the combination of **XARTIGEN** and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of **XARTIGEN** 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

XARTIGEN 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 **XARTIGEN** and fusidic acid should only be considered on a case by case basis and under close medical supervision.

XARTIGEN 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 **XARTIGEN**, 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. **XARTIGEN** 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 **XARTIGEN**.

Race

Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (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 **XARTIGEN** in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating **XARTIGEN** doses in patients treated with protease inhibitors.

The concomitant use with certain protease inhibitors is not recommended unless the dose of **XARTIGEN** 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.

XARTIGEN 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.

Children and adolescents 10 – 17 years of age

The safety profile of rosuvastatin 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.

Lactose intolerance

XARTIGEN contains lactose monohydrate. 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 XARTIGEN:

Transporter protein inhibitors

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

Gemfibrozil and other lipid-lowering products

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

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 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

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 (also see Table 1)

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

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

The maximum daily dose of **XARTIGEN** should be adjusted so that the expected rosuvastatin

exposure would not likely exceed that of a 40 mg daily dose of **XARTIGEN** 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

Interacting medicine dose regimen	**Rosuvastatin dose regime**	**Change in rosuvastatin AUC***
Ciclosporin 75 mg twice daily to 200 mg twice daily, 6 months	10 mg once daily, 10 days	7,1-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 ↑
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 ↑
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 ↑
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	↔
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 XARTIGEN on co-administered medicines:

Warfarin

The pharmacokinetics of warfarin are not significantly affected following co-administration with rosuvastatin. However, as with other HMG-CoA reductase inhibitors, co-administration of **XARTIGEN** 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 **XARTIGEN** 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 rosuvastatin and hormone replacement therapy - therefore, 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, **XARTIGEN** treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

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

XARTIGEN is contraindicated in pregnancy (see section 4.3).

Lactation

XARTIGEN 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).

4.7 Effects on ability to drive and use machines

XARTIGEN may cause dizziness, therefore patients taking **XARTIGEN** should not drive or use

machines until their individual susceptibility to dizziness is known.

4.8 Undesirable effects

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

Table 2: Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY	ADVERSE REACTION
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
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough, dyspnoea
Gastrointestinal disorders	Frequent	Constipation, nausea, abdominal pain
	Less frequent	Pancreatitis
	Frequency unknown	Diarrhoea
Hepatobiliary disorders	Less frequent	Increased hepatic transaminases, jaundice, hepatitis
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, 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 andadministration 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, 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 **XARTIGEN**; 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 administration of **XARTIGEN** is important. It allows continued monitoring of the benefit/risk balance of **XARTIGEN**. Healthcare 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: HMG-CoA reductase inhibitors

ATC code: C10A A07

Mechanism of action

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 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

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.

Metabolism

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 urine.

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 to 2,31-fold elevation in geometric mean $AUC_{(0-t)}$ 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 %) Filipino, 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, 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 in 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 **XARTIGEN** 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 core:

Crospovidone (E1202)

Magnesium oxide (E530)

Magnesium stearate (E572)

Microcrystalline cellulose (E460(i))

Lactose monohydrate

Tablet coating:

Hypromellose (E464)

Lactose monohydrate

Triacetin

Titanium dioxide (E171)

Iron oxide yellow (E172)

XARTIGEN 5: Opadry II Yellow (containing Quinoline yellow aluminium lake (E104); Brilliant blue FCF aluminium lake (E133), Allura red AC aluminium lake (E129), hypromellose (E464), lactose monohydrate, titanium dioxide (E171), triacetin (E1518)).

XARTIGEN 10 / 20: Opadry II Pink (containing Brilliant blue FCF aluminium lake (E133), hypromellose (E464), iron oxide red (E172), lactose monohydrate, titanium dioxide (E171), triacetin (E1518) and Quinoline yellow aluminium lake (E104)).

XARTIGEN 40: Opadry II Pink (containing Allura red AC aluminium lake (E129), Brilliant blue FCF aluminium lake (E133), hypromellose (E464), lactose monohydrate, Sunset yellow FCF aluminium lake (E110), titanium dioxide (E171) and triacetin (E1518)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strips in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Aluminium/aluminium blister strips in a carton containing 10, 30 or 60 tablets.

White high-density polyethylene (HDPE) container with a white opaque polypropylene (PP) cap containing 30, 90 or 500 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Limited

Building 2, Tuscany Office Park,

6 Coombe Place, Rivonia,

Johannesburg, South Africa

8 REGISTRATION NUMBERS

XARTIGEN 5: 50/7.5/0649

XARTIGEN 10: 50/7.5/0650

XARTIGEN 20: 50/7.5/0651

XARTIGEN 40: 50/7.5/0652

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 June 2021

10 DATE OF REVISION OF THE TEXT

To be allocated

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS:

S4

XARTIGEN 5, 5 mg film-coated tablets

XARTIGEN 10, 10 mg film-coated tablets

XARTIGEN 20, 20 mg film-coated tablets

XARTIGEN 40, 40 mg film-coated tablets

Rosuvastatin calcium

Contains sugar: lactose monohydrate

Read all of this leaflet carefully before you start taking XARTIGEN.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, nurse or other healthcare provider.
- **XARTIGEN** has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

1. What **XARTIGEN** is and what it is used for
2. What you need to know before you take **XARTIGEN**
3. How to take **XARTIGEN**
4. Possible side effects
5. How to store **XARTIGEN**
6. Contents of the pack and other information

1. What XARTIGEN is and what it is used for

XARTIGEN contains 5 mg, 10 mg, 20 mg or 40 mg of rosuvastatin, as rosuvastatin calcium, per film-coated tablet and belongs to the pharmacotherapeutic group called HMG-CoA reductase inhibitors.

XARTIGEN is used to reduce the risk of incidents that may cause damage to the heart muscle in patients at risk of developing heart disease as a result of build-up of fats in and on the blood vessels of the heart.

XARTIGEN is used, together with diet, to lower high levels of fats in the blood, which are called lipids, usually when changes to diet and exercise have failed to do this. **XARTIGEN**, in addition to diet, lowers “bad” cholesterol (LDL) and increases “good” cholesterol (HDL) in the blood.

XARTIGEN is also used to reduce total cholesterol and “bad” cholesterol (LDL) in adult patients with very high cholesterol and a family history of high cholesterol, either alone or together with diet and other lipid lowering treatments.

XARTIGEN 40 should only be considered in patients with severe high cholesterol and high cardiovascular risk who do not achieve their treatment goal on 20 mg of **XARTIGEN** or alternative therapy.

Specialist supervision is recommended when the 40 mg dose is initiated.

XARTIGEN can be used in children and adolescents (10 to 17 years of age) to reduce the total cholesterol, “bad” cholesterol (LDL) and lipids in patients with genetically inherited high cholesterol called heterozygous familial hypercholesterolaemia (HeFH).

2. What you need to know before you take XARTIGEN

Do not take XARTIGEN:

- if you are hypersensitive (allergic) to rosuvastatin or any of the other ingredients of **XARTIGEN** (listed in section 6);
- if you currently have a liver disease;
- if you have severe kidney problems;
- if you take a medicine called ciclosporin (used, for example, after organ transplants) (see **Other Medicines and XARTIGEN**);
- if you are pregnant or breastfeeding or if you are a woman of childbearing potential not using appropriate contraceptive measures (see **Pregnancy, breastfeeding and fertility**).

Patients with the following pre-disposing conditions for a muscle disease called myopathy must not take **XARTIGEN 40** (the highest dose). The following conditions may increase the risk of muscle

disorders:

- if you have moderate kidney problems (if in doubt, please ask your doctor);
- if you have a condition called hypothyroidism (underactive thyroid);
- if you have had any 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;
- if you regularly drink large amounts of alcohol;
- if you are taking other medicines called fibrates (for high cholesterol);
- if you are of Asian descent.

Warnings and precautions

Take special care with XARTIGEN.

Tell your doctor or healthcare provider before taking **XARTIGEN**:

- if you have problems with your kidneys;
- if you have unexplained muscle aches and pains, muscle weakness, cramps and especially if you feel unwell or have a fever, tell your doctor immediately;
- if your thyroid gland is not working properly (hypothyroidism);
- if you have a personal or family history of hereditary muscular disorders;
- if you have a previous history of muscle problems when using cholesterol lowering medicines;
- if you regularly consume large amounts of alcohol;
- if you are above 70 years of age;
- if you are taking fibrates (cholesterol lowering medicine) please see **Other medicine and XARTIGEN**;
- 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 **XARTIGEN** can lead to serious muscle problems (rhabdomyolysis), please see **Other medicine and XARTIGEN**.
- if you are taking other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, nicotinic acid, azole antifungals, protease inhibitors (such as lopinavir/ritonavir – medicines used to treat HIV infection) and macrolide antibiotics (see **Other**

medicine and XARTIGEN).

XARTIGEN may cause interstitial lung disease, especially with long-term treatment. Tell your doctor if you experience difficulty breathing, develop a non-productive cough and/or deterioration in general health (e.g. fatigue, weight loss and fever) while taking **XARTIGEN**.
In a small number of people, **XARTIGEN** can affect the liver. This is identified by a 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 treatment starts with **XARTIGEN**, and if needed thereafter.
In patients whose high cholesterol is caused by another disease, such as thyroid or kidney problems, the underlying disease should be treated prior to initiating therapy with **XARTIGEN**.

While you are on **XARTIGEN** 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. **XARTIGEN** should be used with care in patients with Type 2 diabetes and in patients at risk.

Other medicines and XARTIGEN
Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines.)
Tell your doctor if you are taking any of the following medicines:

Contraindicated combinations:
XARTIGEN should not be used together with ciclosporin (used for example, after organ transplants).
The 40 mg dose is contraindicated with concomitant use of a fibrate.

There may be a higher than usual chance of other side effects with:

- Fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe) as these medicines may increase the effect of **XARTIGEN** and the risk of developing serious muscle problems (see **Do not take XARTIGEN** above).
- Fusidic acid (an antibiotic) may increase the risk of developing serious muscle problems (see

Take special care with XARTIGEN above). If you need to take oral fusidic acid to treat a bacterial infection, you will need to temporarily stop using **XARTIGEN**. Your doctor will tell you when it is safe to restart **XARTIGEN**. Taking **XARTIGEN** with fusidic acid may lead to muscle weakness, tenderness or pain (rhabdomyolysis).

- Medicines used to treat viral infections, including HIV or Hepatitis C infection, alone or in combination (please see **Take special care with XARTIGEN** above), as these medicines may increase the effect of **XARTIGEN** and may lead to an increase in the possible side effects of **XARTIGEN**: ritonavir, lopinavir, atazanavir, ombitasvir, paritaprevir, dasabuvir, velpatasvir, razoprevir, elbasvir, glecaprevir, pibrentasvir, darunavir, tipranavir.

Effect of XARTIGEN may be increased with:

- Warfarin or clopidogrel (or any other medicine used for thinning the blood) as **XARTIGEN** may affect the way these medicines work; and clopidogrel may increase the effect of **XARTIGEN**.
- Regorafenib (used to treat cancer) as this may increase the effect of **XARTIGEN**.
- Eltrombopag (used to treat low blood platelet counts caused by an autoimmune disorder) as this may increase the effect of **XARTIGEN**.
- Dronedarone (used to treat abnormal heart rhythm) as this may increase the effect of **XARTIGEN**.
- Itraconazole (used to treat fungal infections) as this may increase the effect of **XARTIGEN**.

Effect of XARTIGEN may be decreased with:

- Indigestion remedies, such as antacids (used to neutralise acid in your stomach) as these medicines may decrease the effect of **XARTIGEN**.
- Erythromycin (an antibiotic) as this may decrease the effect of **XARTIGEN**.

XARTIGEN may increase the effect of other medicines:

- Oral contraceptives (the pill): **XARTIGEN** may increase the effect of contraceptives.
- Hormone replacement therapy: **XARTIGEN** may increase the effect of these medicines.

Taking XARTIGEN with food and alcohol

You can take **XARTIGEN** with or without food.

If you regularly drink large amounts of alcohol, it may increase your risk of muscle disorders.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking **XARTIGEN**.

Women of childbearing potential should use appropriate contraceptive measures. Do not take **XARTIGEN** if you are pregnant or breastfeeding.

Driving and using machines

XARTIGEN may cause dizziness, therefore you should not drive or use machines until you know how **XARTIGEN** affects you.

It is not always possible to predict to what extent **XARTIGEN** may interfere with the daily activities of a patient. You should ensure that you do not engage in the above activities until you are aware of the measure to which **XARTIGEN** affects you.

XARTIGEN contains lactose monohydrate

If you have been told by your doctor that you have intolerance to some sugars, consult your doctor before taking **XARTIGEN**.

XARTIGEN contains Sunset yellow FCF

XARTIGEN contains Sunset yellow FCF which may cause an allergic reaction.

3. How to take XARTIGEN

Do not share medicines prescribed for you with any other person.

Always take **XARTIGEN** exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Before starting treatment, your doctor should place you on a standard cholesterol-lowering diet that should continue during treatment.

The dosage range for **XARTIGEN** is 5 to 40 mg orally once a day. The recommended start dose is 5 mg once a day.

Your dosage will be individualised according to your cholesterol levels, your risk factors and your response to **XARTIGEN** therapy. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 2 to 4-week intervals.

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

For patients with severely high cholesterol (including genetically inherited high cholesterol), a start dose of 20 mg may be considered.

Children and adolescents 10 - 17 years of age

In children and adolescents with genetically inherited high cholesterol, the usual dose range is 5 - 20 mg orally once daily.

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.

For patients with severe renal impairment the dose of **XARTIGEN** should not exceed 10 mg once daily.

Dosage in patients with hepatic insufficiency

The usual starting dose applies in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment should start therapy with **XARTIGEN** 5 mg, doses above 10 mg should be carefully considered.

Race

A 5 mg starting dose of **XARTIGEN** should be considered for Asian patients.

Your doctor will tell you how long your treatment with **XARTIGEN** will last. It may take weeks or months of treatment for you to see any improvement in your symptoms and your symptoms might even worsen when **XARTIGEN** is started. Do not stop treatment early.
If you have the impression that the effect of **XARTIGEN** is too strong or too weak, tell your doctor or pharmacist.

If you take more XARTIGEN than you should

In the event of an overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

If you forget to take XARTIGEN

Do not take a double dose to make up for the forgotten individual doses.

4. Possible side effects

XARTIGEN can have side effects.
Not all side effects reported for **XARTIGEN** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **XARTIGEN**, please consult your healthcare provider for advice.

If any of the following happens, stop taking **XARTIGEN** and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Difficulty in breathing, with or without swelling of the face, lips, tongue and/or throat which may cause difficulty in swallowing, severe itching of the skin (with raised lumps).
- Blistering of the skin, mouth and eyes (Steven-Johnson syndrome).
- Jaundice (yellowing of the skin and eyes).

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to **XARTIGEN**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you

notice any of the following:

- Any unusual aches and pains in your muscles which go on for longer than you might expect, especially if you develop a fever or feel unwell. Unpleasant muscle effects may become a potentially life-threatening muscle damage known as rhabdomyolysis. Muscle symptoms are more frequent in children and adolescents than in adults.
- Tendon disorders sometimes complicated by rupture.
- Serious muscle damage presenting as unexplained muscle aches and pains, feeling unwell and a fever (immune-mediated necrotising myopathy).
- A severe stomach pain (inflamed pancreas).
- Increase in liver enzymes in the blood.
- Hepatitis (an inflamed liver).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects

- Increased glucose levels, diabetes.
- Headache, dizziness.
- Constipation, nausea, stomach pain.
- Muscle pain.
- Feeling weak or a lack of energy.

Less frequent side effects

- Abnormal bleeding or bruising.
- Memory loss.
- Numbness, tingling, loss of sensation in the arms and legs, burning feeling in the hands or feet (polyneuropathy).
- Rash, itching or other skin reactions.
- Oedema (swelling under the skin).
- Cough, shortness of breath, difficulty breathing.
- Lupus-like disease syndrome (including rash, joint disorders and effects on blood cells).

- Muscle rupture.
- Joint pain.
- Traces of blood in your urine.
- Breast enlargement in men (gynaecomastia).

Side effects with unknown frequency

- Depression.
- Diarrhoea.
- An increase in the amount of protein in the urine.
- Numbness and tingling in hands or feet (peripheral neuropathy).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist. You can also report side effects to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: http://www.sahpra.org.za/Publications/Index/8.

By reporting side effects, you can help provide more information on the safety of **XARTIGEN**.

5. How to store XARTIGEN

- Store at or below 25 °C.
- Keep the blister strips in the outer carton until required for use.
- Store all medicines out of reach of children.
- Do not use after the expiry date printed on the label or carton.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets).

6 Contents of the pack and other information

What XARTIGEN contains

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

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

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

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

The other ingredients are:

Tablet core:

Crospovidone (E1202)

Magnesium oxide (E530)

Magnesium stearate (E572)

Microcrystalline cellulose (E460(i))

Lactose monohydrate

Tablet coating:

Hypromellose (E464)

Lactose monohydrate

Triacetin

Titanium dioxide (E171)

Iron oxide yellow (E172)

XARTIGEN 10 / 20: Opadry II Pink (containing Brilliant blue FCF aluminium lake (E133), hypromellose (E464), iron oxide red (E172), lactose monohydrate, titanium dioxide (E171), triacetin (E1518) and Quinoline yellow aluminium lake (E104)).

XARTIGEN 40: Opadry II Pink (containing Allura red AC aluminium lake (E129), Brilliant blue FCF aluminium lake (E133), hypromellose (E464), lactose monohydrate, Sunset yellow FCF aluminium lake (E110), titanium dioxide (E171) and triacetin (E1518)).

What XARTIGEN looks like and contents of the pack

XARTIGEN 5: Yellow, round, biconvex, film-coated tablet, debossed “5” on one side and “R” on other side.

XARTIGEN 10: Pink, round, biconvex, film-coated tablet, debossed “10” on one side and “R” on other

side.

XARTIGEN 20: Pink, round, biconvex, film-coated tablet, debossed “20” on one side and “R” on other side.

XARTIGEN 40: Pink, oval, biconvex, film-coated tablet, debossed “40” on one side and “R” on other side.

Aluminium/aluminium blister strips in a carton containing 10, 30 or 60 tablets.
White high-density polyethylene (HDPE) container with a white opaque polypropylene (PP) cap containing 30, 90 or 500 tablets.

Holder of Certificate of Registration

Accord Healthcare (Pty) Limited

Building 2, Tuscany Office Park,

6 Coombe Place

Rivonia

Johannesburg

South Africa

This leaflet was last revised in

08 June 2021

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