PROFESSIONAL INFORMATION

ROSUZET FILM-COATED TABLETS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROSUZET 5 mg/10 mg (film-coated tablets)

ROSUZET 10 mg/10 mg (film-coated tablets)

ROSUZET 20 mg/10 mg (film-coated tablets)

ROSUZET 40 mg/10 mg (film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROSUZET 5 mg/10 mg

Each film-coated tablet contains 5 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.

ROSUZET 10 mg/10 mg

Each film-coated tablet contains 10 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.

ROSUZET 20 mg/10 mg

Each film-coated tablet contains 20 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.

ROSUZET 40 mg/10 mg

Each film-coated tablet contains 40 mg rosuvastatin (as calcium) and 10 mg of ezetimibe.

Excipients with known effect:

Each ROSUZET 5 mg/10 mg, 10 mg/10 mg, 20 mg/10 mg film-coated tablets contain 200,5 mg of lactose monohydrate and 4,00 mg of sodium.

Each ROSUZET 40 mg/10 mg film-coated tablets contain 205,54 mg of lactose monohydrate and 4,00 mg of sodium.

For the full list of excipients, see section **6.1.**

3. PHARMACEUTICAL FORM

Film-coated tablet

ROSUZET 5 mg/10 mg

Light yellow, round, biconvex film-coated tablets with a diameter of 10 mm approximately and "EL 5" embossed on one side.

ROSUZET 10 mg/10 mg

Beige, round, biconvex film-coated tablets with a diameter of 10 mm approximately and "EL 4" embossed on one side.

ROSUZET 20 mg/10 mg

Yellow, round, biconvex film-coated tablets with a diameter of 10 mm approximately and "EL 3"

embossed on one side.

ROSUZET 40 mg/10 mg

White, round, biconvex film-coated tablets with a diameter of 10 mm approximately and "EL 2" embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROSUZET can be taken as substitution therapy in adult patients adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination, but as separate medicines.

Primary Hypercholesterolaemia

ROSUZET is indicated as adjunctive therapy to diet, when response to diet and exercise is inadequate for the reduction of elevated total cholesterol (total – C) and low-density lipoprotein (LDL – C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Prevention of cardiovascular events

ROSUZET is indicated to reduce the increased risk of cardiovascular disease based on the presence of cardiovascular disease markers such as an elevated high sensitivity c-reactive protein level, age, hypertension, low HDL-C, smoking or family history of premature coronary heart disease.

ROSUZET is indicated to reduce the risk of non-fatal stroke, non-fatal myocardial infarction and

the need for arterial revascularization in patients who are adequately controlled with the individual medicines given concurrently at the same dose level as in the fixed dose combination but as separate products.

4.2 Posology and method of administration

Posology

The patient should be on an appropriate lipid-lowering diet and should continue with this diet during treatment with ROSUZET.

ROSUZET is not suitable for initial therapy. Treatment initiation or dose adjustment, if necessary, should only be done with the monocomponents. After setting the appropriate doses, the switch to the fixed dose combination of the appropriate strength is possible.

Patients should use the strength corresponding to their previous treatment.

The recommended dose is one tablet daily.

ROSUZET 5 mg/10 mg, ROSUZET 10 mg/10 mg and ROSUZET 20 mg/10 mg are not suitable for the treatment of patients requiring a 40 mg dose of rosuvastatin.

Primary hypercholesterolaemia

The usual starting dose is 10 mg of rosuvastatin and 10 mg of ezetimibe once a day. For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a start dose of 20 mg of rosuvastatin may be considered.

Prevention of cardiovascular events

The usual dose is 20 mg of rosuvastatin and 10 mg of ezetimibe once a day.

Dosage in patients taking other medicines

Co-administration with bile acid sequestrants

ROSUZET should be taken either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant (see section **4.5**).

Co-administration with gemfibrozil

Increased systemic exposure to rosuvastatin has been observed in patients taking concomitant rosuvastatin and gemfibrozil.

If ROSUZET is taken in combination with gemfibrozil, the dose of ROSUZET should be limited to 10 mg + mg once daily.

Co-administration with atazanavir and ritonavir, lopinavir and ritonavir or simeprenavir

Initiate ROSUZET therapy with 10 mg + 5 mg once daily. The dose of ROSUZET should not exceed 10 mg + 10 mg once daily.

Co-administration with elbasvir or grazoprevir

The dose of ROSUZET should not exceed 10 mg + 10 mg once daily.

Special populations

Elderly

An initial dose of 5 mg rosuvastatin is recommended in patients > 70 years (see section **4.4**).
The combination is not suitable for initial therapy. Treatment initiation or dose adjustment, if necessary, should only be done with the monocomponents. After setting the appropriate doses, the switch to the fixed dose combination of the appropriate strength is possible.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment.

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

Hepatic impairment

No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment with ROSUZET is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction (see sections **4.4** and **5.2**). ROSUZET is contraindicated in patients with active liver disease (see section **4.3**).

Race

Increased systemic exposure of rosuvastatin has been seen in Asians (see sections **4.4** and **5.2**). The recommended start dose of rosuvastatin is 5 mg for patients of Asian ancestry. ROSUZET 40 mg/10 mg is contraindicated in these patients (see sections **4.3** and **5.2**).

Paediatric population

The safety and efficacy of ROSUZET in children below the age of 18 years has not been established yet.

Method of administration

For oral use.

ROSUZET should be taken once daily, at the same time every day with or without food. The

tablet should be swallowed whole with a drink of water.

4.3 Contraindications

- Hypersensitivity to the active substances (rosuvastatin, ezetimibe) or to any of the excipients of ROSUZET listed in section **6.1.**
- Active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation. exceeding 3 x the upper limit of normal (ULN) (see section **4.4**).
- Pregnancy, breastfeeding and women of childbearing potential not using appropriate contraceptive measures (see section **4.6**).
- Severe renal impairment (creatinine clearance < 30 mL/min) (see section **5.2**).
- In patients with myopathy (see section **4.4**).
- In patients receiving concomitant ciclosporin (see section **4.5**).
- Moderate to severe hepatic impairment (Child Pugh 7 or more)
- Patients taking fusidic acid.

The 40 mg/10 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 plasma levels of rosuvastatin 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

Skeletal Muscle Effects

Effects on skeletal muscle e.g., myalgia, myopathy, and rhabdomyolysis have been reported in rosuvastatin-treated patients with all doses and in doses with > 20 mg. As with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis associated with rosuvastatin in post-marketing use is higher at the 40 mg dose.

In post-marketing experience with ezetimibe, cases of myopathy and rhabdomyolysis have been reported. However, rhabdomyolysis has been reported very rarely with ezetimibe monotherapy and very rarely with the addition of ezetimibe to other medicines known to be associated with increased risk of rhabdomyolysis.

If myopathy is suspected based on muscle symptoms or is confirmed by a creatine kinase level, ROSUZET and any of these medicines known to be associated with increased risk of rhabdomyolysis, that the patient is taking concomitantly should be immediately discontinued. All patients starting should be told to report promptly any unexplained muscle pain, tenderness or weakness (see section **4.8**).

Creatine Kinase Measurement

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

Before treatment

ROSUZET, as other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis.

Such factors include:

- Renal impairment.
- Hypothyroidism.
- Personal or family history of hereditary muscular disorders.
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate.
- Alcohol abuse.
- Age > 70 years.
- Situations where an increase in plasma levels may occur (see section **4.2**, **4.5** and **5.2**).
- Concomitant use of fibrates.

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

Whilst on treatment

Patients should be asked to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy should be discontinued if CK levels are markedly elevated (> 5x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5x ULN). If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing rosuvastatin or an alternative HMG-CoA reductase inhibitor at the lowest dose with close monitoring of the patient. 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 characterized by proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment.

In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with fibric acid derivatives including gemfibrozil, ciclosporin, azole antifungals, protease inhibitors and macrolide antibiotics. Gemfibrozil increases the risk of myopathy when given concomitantly with some HMG-CoA reductase inhibitors. Therefore, the combination of ROSUZET and gemfibrozil is not recommended. The combination of ROSUZET and other fibrates (except fenofibrate) is not recommended. The 40 mg dose of rosuvastatin is contradicted with concomitant use of a fibrate (see sections **4.3**, **4.5** and **4.8**).

ROSUZET should not be used in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypertension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders or uncontrolled seizures).

Liver effects

In controlled co-administration trials in patients receiving ezetimibe with a statin, consecutive transaminase elevations (≥ 3 x the upper limit of normal [ULN]) have been observed.

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

Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, ROSUZET is not recommended (see section **5.2**).

Liver disease and alcohol

ROSUZET should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with higher doses of rosuvastatin, particularly 40 mg, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of 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 should be considered during routine follow-up of patients treated with a dose of 40 mg.

Interstitial lung disease

Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy (see section **4.8**). Presenting features can include dyspnoea, non-productive cough and deterioration in general health (fatigue, weight loss and fever). If it is suspected a patient has developed interstitial lung disease, statin therapy should be discontinued.

Diabetes mellitus

Some evidence suggests that statins as a class raise blood glucose, and in some patients at higher risk of future diabetes, may produce a level of hyperglycaemia where formal diabetes care is appropriate.

However, the risk is outweighed by the reduction in vascular risk with statins and therefore, should not be a reason for stopping statin treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/L, BMI > 30 kg/m^2, raised triglycerides, hypertension) should be monitored both clinically and biochemically according to national guidelines.

Parasomnias

Statins, as in ROSUZET, may cause various parasomnias. Parasomnia is an umbrella term for complex movements or behaviours during sleep, including abnormal dreaming, nightmares (paroniria) and sleepwalking (somnambulism).

The Centre for Adverse Reactions Monitoring (CARM) received over 70 reports of various parasomnias over a period of five years. The most frequently reported terms are abnormal dreams, paroniria and sleep disorder. Commonly reported medicines include statins, varenicline and montelukast.

Anticoagulants

If ROSUZET is added to warfarin, another coumarin anticoagulant or fluindione, the International Normalised Ratio (INR) should be appropriately monitored (see section **4.5**).

Ciclosporin

See section **4.3** and **4.5**.

Fibrates

The safety and efficacy of ezetimibe administered with fibrates have not been established (see above and sections **4.3** and **4.5**). If cholelithiasis is suspected in a patient receiving ROSUZET and fenofibrate, gallbladder investigations are indicated, then this therapy should be discontinued (see sections **4.5** and **4.8**).

Fusidic acid

ROSUZET 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**). The patient should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. ROSUZET therapy may be re-introduced seven days after the last dose of fusidic acid.

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 ROSUZET in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up titrating rosuvastatin in patients treated with protease inhibitors. The concomitant use with certain protease inhibitors is not recommended unless the dose is adjusted (see sections **4.2** and **4.5**).

Race

Rosuvastatin pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians (see sections **4.2**, **4.3** and **5.2**).

Paediatric population

The safety and efficacy of ROSUZET in children below the age of 18 years has not been established yet, therefore its use is not recommended in this age group.

ROSUZET contains lactose

Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take

ROSUZET.

ROSUZET contains sodium

ROSUZET contains less than 1 mmol sodium (23 mg) per tablet, that is to say, “essentially sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications

Ciclosporin

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

In a study of eight post-renal transplant patients with creatinine clearance of > 50 mL/min on a stable dose of ciclosporin, a single 10-mg dose of ezetimibe resulted in a 3,4-fold (range 2,3 to 7,9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population receiving ezetimibe alone from another study. In a different study, a renal transplant patient with severe renal insufficiency who was receiving ciclosporin and multiple other medications, demonstrated a 12- fold greater exposure to total ezetimibe compared to concurrent controls receiving ezetimibe alone. In a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100 mg dose of ciclosporin on Day 7 resulted in a mean 15 % increase in ciclosporin AUC (range 10 % decrease to 51 % increase) compared to a single 100 mg dose of ciclosporin alone. A controlled study on the effect of co-administered ezetimibe on ciclosporin exposure in renal transplant patients has not been

conducted.

Not-recommended combinations

Protease inhibitors

Although the exact mechanism of interaction is unknown, concomitant protease inhibitor use may strongly increase rosuvastatin exposure (see section **4.5**). For instance, in a pharmacokinetic study, co-administration of 10 mg rosuvastatin and a combination product of two protease inhibitors (300 mg atazanavir / 100 mg ritonavir) in healthy

volunteers were associated with an approximately three-fold and seven-fold increase in rosuvastatin AUC and C_{max} respectively.

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

Transporter protein inhibitors

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of ROSUZET with medicinal products 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**).

Gemfibrozil and other lipid-lowering products

Concomitant use of rosuvastatin, as in ROSUZET, and gemfibrozil resulted in a 2-fold increase

in rosuvastatin C_{max} and AUC (see section **4.4**). Concomitant gemfibrozil administration increased total ezetimibe concentrations (approximately 1.7-fold). Based on data from specific interaction studies no pharmacokinetic relevant interaction between rosuvastatin and fenofibrate is expected, however a pharmacodynamic interaction may occur. Concomitant fenofibrate administration increased total ezetimibe concentrations (approximately 1.5- fold). Fenofibrate, and other fibrates increase the risk of myopathy when given concomitantly with HMG- CoA reductase inhibitors probably because they can produce myopathy when given alone.

In patients receiving fenofibrate and ezetimibe, medical practitioners should be aware of the possible risk of cholelithiasis and gallbladder disease (see section **4.4** and **4.8**). If cholelithiasis is suspected in a patient receiving ezetimibe and fenofibrate, gallbladder investigations are indicated. This therapy should be discontinued (see section **4.8**). Co-administration of ezetimibe with other fibrates have not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In animal studies, ezetimibe sometimes increased cholesterol in the gallbladder bile, but not all species (see section **5.3**). A lithogenic risk associated with the therapeutic use of ezetimibe cannot be ruled out. The 40 mg/10 mg dose is contraindicated with concomitant use of a fibrate (see sections **4.3** and **4.4**).

Fusidic Acid

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with statins, as in ROSUZET. 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, ROSUZET treatment should be discontinued throughout the duration of the fusidic acid treatment (see section **4.4**).

Other interactions

Antacid

The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50 %. This effect was mitigated when the antacid was dosed 2 hours after rosuvastatin. The clinical relevance of this interaction has not been studied. Concomitant antacid administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

Erythromycin

Concomitant use of rosuvastatin and erythromycin resulted in a 20 % decrease in AUC_{0-t} and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gut motility caused by erythromycin.

Cytochrome P450 enzymes

Results from *in vitro* and *in vivo* studies show that rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, rosuvastatin is a poor substrate for these isoenzymes. Therefore, 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). In preclinical studies, it has been shown that ezetimibe does not induce cytochrome P450 drug metabolizing enzymes. No clinically significant pharmacokinetic interactions have been observed between ezetimibe and medicines known to be metabolised by cytochromes P450 1A2, 2D6, 2C8, 2C9, and 3A4, or N-acetyltransferase.

Vitamin K antagonists

The initiation of treatment or dosage up-titration of rosuvastatin in patients treated concomitantly with vitamin K antagonists (e.g., warfarin or another coumarin anticoagulant) may result in an increase in International Normalized Ratio (INR). Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Concomitant administration of ezetimibe (10 mg once daily) had no effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. However, there have been post-marketing reports of increased International Normalised Ratio (INR) in patients who had ezetimibe added to warfarin or fluindione. If ROSUZET is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored (see section **4.4**).

Oral contraceptive/hormone replacement therapy (HRT)

Concomitant use of rosuvastatin, as in ROSUZET, and 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 is no pharmacokinetic data available in subjects taking concomitant rosuvastatin and HRT and therefore a similar effect cannot be excluded. However, the combination has been extensively used in women in clinical trials and was well tolerated. In clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Cholestyramine

Concomitant cholestyramine administration decreased the mean area under the curve (AUC) of total ezetimibe (ezetimibe + ezetimibe glucuronide) approximately 55%. The incremental low-density lipoprotein cholesterol (LDL-C) reduction due to adding ezetimibe to cholestyramine

may be lessened by this interaction (see section **4.2**). Therefore, dosing of ROSUZET and a bile acid sequestrant should take place several hours apart.

Ezetimibe/rosuvastatin

Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1.2-fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out (see section **4.4**).

Other medicinal products

Based on data from specific interaction studies no clinically relevant interaction between rosuvastatin and digoxin is expected in clinical interaction studies, ezetimibe had no effect on the pharmacokinetics of dapsone, dextromethorphan, digoxin, glipizide, tolbutamide or midazolam during co-administration. Cimetidine co-administered with ezetimibe had no effect on the bioavailability of ezetimibe.

Inhibitors of Breast Cancer Resistance Protein (BCRP)

Concomitant administration of medicines that are inhibitors of BCRP e.g., elbasvir and grazoprevir) may lead to increased plasma concentrations of rosuvastatin, as in ROSUZET, and an increased risk of myopathy. Therefore, the dose of ROSUZET should not exceed 10 mg ezetimibe + 10 mg rosuvastatin once daily in patients receiving concomitant medicines containing elbasvir or grazoprevir.

Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with HMG-CoA reductase inhibitors, including rosuvastatin, co-administered with colchicine, and caution should be

exercised when prescribing ROSUZET with colchicine.

Daptomycin

The risk of myopathy and/or rhabdomyolysis may be increased by concomitant administration of HMG-CoA reductase inhibitors such as ROSUZET and daptomycin.

Ticagrelor

Cases of rhabdomyolysis have been reported in patients taking rosuvastatin, as in ROSUZET, with ticagrelor. The patients who developed rhabdomyolysis were high-risk patients, namely elderly with initially an excessive dose of rosuvastatin, and some patients taking ezetimibe as concomitant therapy.

One form of interaction is a worsening of the renal function caused by ticagrelor, resulting in the rise of plasma concentration of rosuvastatin, which then causes rhabdomyolysis.

The other possibility or additional type can be the pharmacogenomics polymorphism and interaction on the level of the transporters, which can raise the rosuvastatin level.

Patients who have developed elevated creatinine kinase levels without clinical symptoms and patients with myositis who were also given rosuvastatin, as in ROSUZET, should be further assessed.

Interactions requiring rosuvastatin dose adjustments

When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products. For example, a 20 mg dose of rosuvastatin with gemfibrozil (1,9-fold

increase) and a 10 mg dose of rosuvastatin with combination atazanavir/ritonavir (3,1-fold increase).

4.6 Fertility, pregnancy and lactation

ROSUZET is contraindicated in pregnancy and breast-feeding (see section **4.3**).

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures. ROSUZET should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential risk. If the patient becomes pregnant while taking ROSUZET, therapy should be discontinued, and the patient apprised of the potential hazard to the foetus.

Pregnancy

Rosuvastatin

Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of ROSUZET, treatment should be discontinued immediately.

Ezetimibe

No clinical data is available on the use of ezetimibe during pregnancy. Animal studies on the use of ezetimibe in monotherapy have shown no evidence of direct or indirect harmful effects on pregnancy, embryofoetal development, birth or postnatal development.

Breastfeeding

Rosuvastatin

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

Ezetimibe

Studies on rats have shown that ezetimibe is secreted into milk. It is not known if ezetimibe is secreted into human breast milk.

Fertility

No clinical trial data is available on the effects of ezetimibe or rosuvastatin on human fertility. Ezetimibe had no effect on the fertility of male or female rats. Rosuvastatin at higher doses showed testicular toxicity in monkeys and dogs.

4.7 Effects on ability to drive and use machines

ROSUZET has no or negligible influence on the ability to drive and use machines. Studies to determine the effect of rosuvastatin and/or ezetimibe on the ability to drive and use machines have not been conducted. However, when driving vehicles or operating machines, it should be considered that dizziness may occur during treatment. Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that ROSUZET do not adversely affect their ability to do so safely.

4.8 Undesirable effects

Summary of the safety profile.

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

Tabulated list of adverse reactions

The frequencies of adverse events are ranked according to the following:

Frequent = (≥ 1/100 to < 1/10).

Less frequent = Infrequent (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (<1/10,000).

Frequency not known = cannot be estimated from the available data.

MedDRA SOC	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders		thrombo-cytopenia[2]	thrombo-cytopenia[5]
Immune system disorders		hypersensitivity reactions including angioedema[2]	hypersensitivity (including rash, urticaria, anaphylaxis and angioedema)[5]
Endocrine disorders	diabetes melitus[1,2]		
Metabolism and Nutrition disorders		decreased appetite[3]	
Psychiatric disorders			depression[2,5]
Nervous system disorders	headache[2,4], dizziness[2]	paraesthesia[4], polyneuropathy[2], memory loss[2]	Peripheral neuropathy[2], sleep disturbances (including insomnia and nightmares)[2], dizziness[5], paraesthesia[5]
Vascular disorders		hot flush[3], hypertension[3]	
Respiratory, thoracic and mediastinal disorders		cough[3]	cough[2], dyspnoea[2,5]
Gastrointestinal disorders	constipation[2], nausea[2], abdominal pain[2,3], diarrhoea[3], flatulence[3]	dyspepsia[3], gastro-oesophageal reflux disease[3], nausea[3], dry mouth[4], gastritis pancreatitis[2]	diarrhoea[2], pancreatitis[5], constipation[5]
Hepatobiliary disorders		increased hepatic transaminases[2] , jaundice[2], hepatitis[2]	hepatitis[5], cholelithiasis[5], cholecystitis[5]

Skin and subcutaneous tissue disorders		pruritus[2,4], rash[2,4], urticaria[2,4]	Stevens-Johnson syndrome[2], erythema multiforme[5]
Musculoskeletal and connective tissue disorders	myalgia[2,4]	arthralgia[3], muscle spasms[3], neck pain[3], back pain[4], muscular weakness[4], pain in extremity[4] myopathy (including myositis)[2], rhabdomyolysis[2], lupus-like syndrome[2], muscle-rupture[2] ,arthralgia[2]	immune-mediated necrotising myopathy[2], tendon disorders, sometimes complicated by rupture[2], arthralgia[5], myalgia[5], myopathy/rhabdomyolysis[5] (see section 4.4)
Renal and urinary disorders		haematuria[2]	
Reproductive system and breast disorders		Gynecomastia[2]	
General disorders and administration site conditions	asthenia[2], fatigue[3]	chest pain[3], pain[3], asthenia[4], oedema peripheral[4]	oedema[2], asthenia[5]
Investigations	ALT and/or AST increased[4]	ALT and/or AST increased[3], blood CPK increased[3], gamma-glytamyl-transferase increased[3], liver function test abnormal[3]	

[1] Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI>30kg/m2, raised triglycerides, history of hypertension) – for rosuvastatin.

[2] Adverse reaction profile for rosuvastatin based on data from clinical studies and extensive post- marketing experience.

[3] Ezetimibe in monotherapy. Adverse reactions were observed in patients treated with ezetimibe (N=2396) and at a greater incidence than placebo (N=1159)

[4] Ezetimibe co-administered with a statin. Adverse reactions were observed in patients with ezetimibe co-administered with a statin (N=11308) and at a greater incidence than statin administered alone (N=9361).

[5] Additional adverse reactions of ezetimibe, reported in post-marketing experience (with or without statin).

Description of selected adverse reactions

Renal effects

Proteinuria, detected by dipstick testing and mostly tubular in origin has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in <1 % of patients sometime during treatment with 10 and 20 mg and in approximately 3 % of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy.

Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease. Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal Muscle Effects

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

A dose-related increase in CK levels has been observed in patients taking rosuvastatin. Most cases were mild, asymptomatic and transient. If CK-levels are elevated (> 5x ULN), the 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; most 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) are higher at the 40 mg rosuvastatin dose.

Laboratory values

In controlled clinical monotherapy trials, the incidence of clinically important elevations in serum transaminases (ALT and/or AST ≥ 3 X ULN, consecutive) was similar between ezetimibe (0,5 %) and placebo (0,3%). In co-administration trials, the incidence was 1,3% for patients treated with ezetimibe co-administered with a statin and 0,4 % for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment (see section **4.4**).

In clinical trials, CPK > 10 X ULN was reported for 4 of 1,674 (0,2 %) patients administered ezetimibe alone vs 1 of 786 (0,1 %) patients administered placebo and for 1 of 917 (0,1 %) patients co- administered ezetimibe and a statin vs 4 of 929 (0,4 %) patients administered a statin alone. There was no excess of myopathy or rhabdomyolysis associated with ezetimibe compared with the relevant control arm (placebo or statin alone) (see section **4.4)**.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

In the event of an overdose, side effects can be precipitated and/or be of increased severity

(see section **4.8**).

Treatment

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. Haemodialysis is unlikely of benefit. In symptomatic patients, monitor serum creatinine, BUN, creatinine phosphokinase and urine myoglobin for indications of renal impairment secondary to rhabdomyolysis. Liver function tests should be performed in symptomatic patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A.7.5 Serum-cholesterol reducers

Pharmacotherapeutic group: HMG CoA reductase inhibitors in combination with other lipid modifying agents.

ATC code: C10BA06

Mechanism of action

ROSUZET contains ezetimibe and rosuvastatin, two lipid-lowering compounds with complementary mechanisms of action. ROSUZET reduces elevated total cholesterol (total-C), LDL-C, apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and increases high-density lipoprotein cholesterol (HDL-C) through dual inhibition of cholesterol absorption and synthesis.

Rosuvastatin 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 increases the number of hepatic LDL receptors on the cell- surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

Pharmacodynamic effects

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, nonHDL-C, VLDL-C, VLDL-TG and increases ApoA-I . Rosuvastatin also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.

Ezetimibe mechanism of action

Ezetimibe selectively inhibits the intestinal absorption of cholesterol and related plant sterols. Ezetimibe is orally active and has a mechanism of action that differs from other classes of cholesterol-reducing compounds (e.g., statins, bile acid sequestrants [resins], fibric acid derivatives, and plant stanols). The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

Ezetimibe localises at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. Statins reduce cholesterol synthesis in the liver and together these distinct mechanisms provide complementary cholesterol reduction. In a 2-week clinical study in 18 hypercholesterolaemic patients, ezetimibe inhibited intestinal cholesterol absorption by 54 %, compared with placebo.

Pharmacodynamic effects

Ezetimibe inhibited the absorption of [^{14}C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol or fat soluble vitamins A and D.

Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Administration of ezetimibe with a statin is effective in reducing the risk of cardiovascular events in patients with coronary heart disease and ACS event history.

5.2 Pharmacokinetic properties

Rosuvastatin and ezetimibe combination therapy

Concomitant use of 10 mg rosuvastatin and 10 mg ezetimibe resulted in a 1,2 fold increase in AUC of rosuvastatin in hypercholesterolaemic subjects. A pharmacodynamic interaction, in terms of adverse effects, between rosuvastatin and ezetimibe cannot be ruled out.

Rosuvastatin

Absorption

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

Distribution

Rosuvastatin is taken up extensively by the liver, which is the primary site of cholesterol synthesis and LDL-C clearance. The volume of distribution of rosuvastatin is approximately 134

L. Approximately 90 % of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation

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

Elimination

Approximately 90% of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5 % is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21,7 %).

As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity

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

Special populations

Age and sex

There were no clinically relevant effects of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolaemia appears to be similar to or lower than that in adult patients with dyslipidaemia.

Race

Pharmacokinetic studies show an approximate 2-fold elevation in, median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}.

A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal impairment

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

Hepatic impairment

In a study with subjects with varying degrees of hepatic impairment there was no evidence of

increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child-Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores.

There is no experience in subjects with Child-Pugh scores above 9.

Genetic polymorphisms

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

Paediatric population

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

Ezetimibe

Absorption

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Mean maximum plasma concentrations (C_{max}) occur within 1 to 2 hours for ezetimibe-glucuronide and 4 to 12 hours for ezetimibe. The absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. Concomitant food administration (high fat or non-fat meals) had no effect on the oral bioavailability of ezetimibe. Ezetimibe can be administered with or without food.

Distribution

Ezetimibe and ezetimibe-glucuronide are bound 99,7 % and 88 to 92 % to human plasma proteins, respectively.

Biotransformation

Ezetimibe is metabolised primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10 to 20 % and 80 to 90 % of the total medicine in plasma, respectively. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Elimination

Following oral administration of ^{14}C-ezetimibe (20 mg) to human subjects, total ezetimibe accounted for approximately 93 % of the total radioactivity in plasma. Approximately 78 % and 11 % of the administered radioactivity was recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the

plasma.

Special populations

Age and sex

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with ezetimibe. Therefore, no dosage adjustment is necessary in the elderly. Plasma concentrations for total ezetimibe are slightly higher (approximately 20 %) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary based on gender.

Renal impairment

After a single 10 mg dose of ezetimibe in patients with severe renal disease mean CrCl ≤ 30 mL/min/1.73m^2) the mean AUC for total ezetimibe was increased approximately 1,5- fold, compared to healthy subjects. This result is not considered clinically significant. No dosage adjustment is necessary for renally impaired patients.

An additional patient in this study (post-renal transplant and receiving multiple medications, including ciclosporin) had a 12-fold greater exposure to total ezetimibe.

Hepatic impairment

After a single 10 mg dose of ezetimibe, the mean AUC for total ezetimibe was increased approximately 1,7-fold in patients with mild hepatic insufficiency (Child Pugh score 5 or 6), compared to healthy subjects. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency (Child Pugh score 7 to 9), the mean AUC for total ezetimibe was

increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe (Child Pugh score >9) hepatic insufficiency, ROSUZET is not recommended in these patients (see section **4.4**).

Paediatric population

The pharmacokinetics of ezetimibe are similar between children ≥ 6 years and adults. Pharmacokinetic data in the paediatric population < 6 years of age are not available. Clinical experience in paediatric and adolescent patients includes patients with HoFH, HeFH, or sitosterolaemia.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

- Lactose monohydrate
- Croscarmellose Sodium (E468)
- Povidone
- Sodium Laurilsulfate (E487)
- Cellulose, Microcrystalline 102
- Hypromellose 2910 (E464)
- Silica, Colloidal Anhydrous
- Magnesium stearate (E470).

Tablet Coating

ROSUZET 5 mg/10 mg - Opadry Yellow 02F220026 consisting of:

- Hypromellose 2910 (E464)
- Macrogol 4000 (E1521)
- Titanium dioxide (E171)
- Iron oxide yellow (E172)
- Talc (E553b)
- Iron oxide red (E172).

ROSUZET 10 mg/10 mg - Opadry Beige 02F270003 consisting of:

- Hypromellose 2910 (E464)
- Titanium dioxide (E171)
- Iron oxide yellow (E172)
- Macrogol 4000 (E1521)
- Talc (E553b).

ROSUZET 20 mg/10 mg - VIVACOAT PC-2P-308 consisting of:

- Hypromellose 6 (E464)
- Titanium dioxide (E171)
- Talc (E553b)
- Polyethylene glycol (PEG) (E1521)
- Iron oxide yellow (E172).

ROSUZET 40 mg/10 mg - Opadry White OY-L-28900 consisting of:

- Lactose monohydrate
- Hypromellose 2910 (E464)
- Titanium dioxide (E171)
- Macrogol 4000 (E1521).

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 temperature storage conditions. Store in the original package in order to protect from moisture and light.

6.5 Nature and contents of container

OPA/Al/PVC//Al blisters packed into carton boxes.

Pack size of 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap,

Mispel Street, Belville

7530

Customer Care: 080 222 6662

8. MARKETING AUTHORISATION NUMBER(S)

ROSUZET 5 mg/10 mg – 55/7.5/0224

ROSUZET 10 mg/10 mg – 55/7.5/0225

ROSUZET 20 mg/10 mg – 55/7.5/0226

ROSUZET 40 mg/10 mg – 55/7.5/0227

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 November 2022

10. DATE OF REVISION OF THE TEXT

TBA