Selected Safety Information for ROSUZET® Composite Pack (ezetimibe tablets and rosvastatin tablets)

Based on Product Information approved by the TGA on 26 November 2014

**Indications**

**Primary Hypercholesterolaemia**
ROSUZET Composite Pack is indicated as adjunctive therapy to diet in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia where use of a combination product is appropriate in those patients:
- not appropriately controlled with atorvastatin or ezetimibe alone; or
- already treated with atorvastatin and ezetimibe

**Homozygous Familial Hypercholesterolaemia (HoFH)**
ROSUZET Composite Pack is indicated in patients with HoFH. Patients may also receive adjunctive treatments (e.g. LDL apheresis).

**Dosage and Administration**

This combination product is not indicated for first-line use.

ROSUZET Composite Pack can be administered within the dosage range of 10 mg + 5 mg to 10 mg + 40 mg as a single daily dose. The recommended starting dose is 10 mg + 5 mg or 10 mg + 10 mg once per day. A dose adjustment can be made after 4 weeks of therapy where necessary. The usual maximum dose of rosvastatin is 20 mg once per day.

A dose of 40 mg rosvastatin once per day should only be considered in patients who are still at high cardiovascular risk after their response to a dose of 20 mg once per day is assessed. This may particularly apply to patients with familial hypercholesterolaemia. It is recommended that the 40 mg dose is used only in patients in whom regular follow-up is planned. A dose of 40 mg rosvastatin must not be exceeded in any patient. Specialist supervision should be considered when the dose is titrated to 40 mg.

**Hepatic Insufficiency**
There may be increased exposure to rosvastatin in patients receiving the combination. The lowest effective dose should be used and regular monitoring for adverse effects should be performed. No dosage adjustment is required in patients with mild hepatic insufficiency (Child Pugh score 5 to 6). Treatment is not recommended in patients with moderate (Child Pugh score 7 to 9) or severe (Child Pugh score > 9) liver dysfunction.

**Renal Insufficiency**
There may be increased exposure to rosvastatin in patients receiving this combination. The lowest effective dose should be used and regular monitoring for adverse effects should be performed. No dosage adjustment is required for patients with mild to moderate renal impairment. For patients with severe renal impairment (CLcr<30 mL/min/1.73m²) not on dialysis the dose of rosvastatin should be started at 5 mg once daily and not exceed 10 mg once daily.
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.

**Dosage in Asian patients**

Initiation of therapy with ROSUZET Composite Pack 10 mg + 5 mg once daily should be considered for Asian patients. The potential for increased systemic exposures relative to Caucasians is relevant when considering escalation of dose in cases where hypercholesterolaemia is not adequately controlled at doses of 10 + 5 mg, 10 + 10 mg or 10 + 20 mg once daily.

In patients taking cyclosporin, ROSUZET Composite Pack dosage should be limited to 10 mg + 5 mg once daily.

**Contraindications**

- Known hypersensitivity to any component of this medication
- Myopathy secondary to other lipid lowering agents
- During pregnancy, in nursing mothers and in women of childbearing potential, unless they are taking adequate contraceptive precautions
- Active liver disease including unexplained persistent elevations in serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN)
- In combination with fenofibrate in patients with gall bladder disease
- Concomitant use of fusidic acid

Due to the rosuvastatin 40mg component, ROSUZET 10 mg + 40 mg is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:

- 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
- Severe renal impairment (CrCl < 30 mL/min)
- Asian patients
- Concomitant use of fibrates.

**Precautions**

There is limited long term safety data of ROSUZET Composite Pack. Due to risk factors such as hepatic or renal impairment that may increase rosuvastatin exposure and the potential for increased adverse effects at the highest dose (10 mg + 40 mg) (e.g. muscle effects, renal impairment and elevated liver enzymes), monitoring of patients on the highest dose of ROSUZET Composite Pack is recommended.

The incidence of persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0, 0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the
elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. **Liver function tests should be performed before initiation of treatment and periodically thereafter.** Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of **ROSUZET Composite Pack** is recommended.

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

**Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in rosvastatin treated patients. Creatine kinase (CK) elevations (> 10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosvastatin at doses up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values > 10 times upper limit of normal, was reported in up to 0.1% of patients taking rosvastatin doses of up to 40 mg in clinical studies. As with other HMG-CoA reductase inhibitors, reports of rhabdomyolysis with rosvastatin are rare, but higher at the highest marketed dose (40 mg).

Consequently:

1. **ROSUZET Composite Pack** should be prescribed with caution in patients with predisposing factors for myopathy, such as renal impairment, advanced age and hypothyroidism.
2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **ROSUZET Composite Pack** therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.
3. Rosuvastatin 40 mg is reserved only for those patients who are not adequately controlled at the 20 mg dose, considering their level of LDL-C and overall CV risk profile. Similarly, **ROSUZET Composite Pack** 10mg + 40mg should be reserved for such patients.
4. The risk of myopathy during treatment with rosvastatin may be increased with concurrent administration of other lipid-lowering therapies, protease inhibitors, or cyclosporin. The benefit of further alterations in lipid levels by the combined use of **ROSUZET Composite Pack** with niacin should be carefully weighed against the potential risks of this combination. Combination therapy with **ROSUZET Composite Pack** and gemfibrozil should generally be avoided. The combination of **ROSUZET** and other fibrates (except fenofibrate) is not recommended.
5. The risk of myopathy during treatment with **ROSUZET Composite Pack** may be increased in circumstances that increase rosvastatin drug levels
6. **ROSUZET COMPOSITE PACK** therapy should also be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, or uncontrolled seizures).
There have been very rare reports of an immune-mediated necrotising myopathy clinically characterised by persistent proximal muscle weakness and elevated serum creatine kinase during treatment or following discontinuation of statins, including rosuvastatin. Additional neuromuscular and serologic testing may be necessary. Treatment with immunosuppressive agents may be required.

The long term safety and efficacy of rosuvastatin treatment in patients commencing treatment with LDL-C < 3.4 mmol/L who have been assessed to be at risk of cardiovascular events have not been established. Data are currently available for up to 2 years for the 20 mg dose only. The risk benefit balance for longer term use of rosuvastatin in this population has therefore not been established. The benefits of longer term treatment should be weighed against safety and tolerability risks.

Increases in HbA1c and serum glucose levels have been observed in patients treated with rosuvastatin. An increased frequency of diabetes mellitus has been reported with rosuvastatin in patients with risk factors for diabetes mellitus.

The result of a large pharmacokinetic study conducted in the US demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) compared with a Caucasian control group. This increase should be considered when making ROSUZET Composite Pack dosing decisions for Asian patients.

**Interactions with Other Medicines**

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

Fusidic acid must not be co-administered with statins. There have been reports of rhabdomyolysis (including some fatalities) in patients receiving this combination. In patients where the use of systemic fusidic acid is considered essential, ROSUZET Composite Pack treatment should be discontinued throughout the duration of fusidic acid treatment and may be re-introduced seven days after the last dose of fusidic acid.

Caution should be exercised if ROSUZET Composite Pack is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spironolactone, and cimetidine.

The co-administration of ezetimibe with fibrates, other than fenofibrate, has not been studied. Therefore, co-administration of ROSUZET Composite Pack and fibrates is not recommended.

Caution should be exercised when initiating ROSUZET Composite Pack in the setting of cyclosporin. Cyclosporin concentrations should be monitored in patients receiving ROSUZET Composite Pack and cyclosporin.
If ROSUZET Composite Pack is added to warfarin or another coumarin anticoagulant, the International Normalised Ratio (INR) should be appropriately monitored.

The dosing of ROSUZET Composite Pack and a bile acid binding sequestrant should take place several hours apart. However, efficacy and safety of such combination have not been studied.

Increased systemic exposure to rosuvastatin has been observed in subjects receiving rosuvastatin with various protease inhibitors in combination with ritonavir. Consideration should be given both to the benefit of lipid lowering by the use of ROSUZET Composite Pack in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating ROSUZET Composite Pack doses in patients treated with protease inhibitors.

**Adverse Effects**

In a 6 week-active comparator study (P139V1), 440 subjects taking rosuvastatin (5 mg or 10 mg) were randomised to either rosuvastatin (10 mg or 20 mg) or ezetimibe 10 mg added to rosuvastatin (5 or 10 mg) therapy, equivalent to ROSUZET Composite Pack 10 mg + 5mg or 10mg + 10 mg. The co-administration was generally well tolerated. The drug-related adverse events reported in the ROSUZET Composite Pack 10 mg + 5mg or 10mg + 10 mg group were abdominal distension, abdominal pain, constipation, dry mouth, nausea, arthralgia, myalgia, allergic dermatitis and eczema.

In this study, the incidence of clinically important elevations in serum transaminases (ALT ≥3 X ULN, consecutive) was 0.5% (n=1) for patients treated with ezetimibe + rosuvastatin and 0% for patients in the rosuvastatin only treatment group. No patients in either group had clinically significant elevations in AST. Clinically important elevations in creatine kinase (CK ≥10 X ULN) were seen in 0.5% (n=1) of patients in the rosuvastatin only treatment group and not seen in patients treated with ezetimibe + rosuvastatin.

In another 6 week randomised active-comparator study (EXPLORER) in 469 subjects with hypercholesterolemia and a history of CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score > 20%), the incidence of increased ALT at the 10 mg + 40 mg dose was 2.5% (n=6) for ezetimibe + rosuvastatin and 0.4% (n=1) for rosuvastatin alone.

**Use in Special Populations**

**Use in the Elderly**

No dosage adjustment is required for elderly patients. ROSUZET Composite Pack should be prescribed with caution in the elderly.

**Use in Paediatric Patients**

Not recommended for use in children.

**Pregnancy and lactation**

ATOZET Composite Pack is contraindicated during pregnancy and lactation.

**For more information on indications, contraindications, precautions, interactions with other medicines, and adverse effects, please consult the full Product Information.**