SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TOROLAR 5 (5 mg film-coated tablets)
TOROLAR 10 (10 mg film-coated tablets)
TOROLAR 20 (20 mg film-coated tablets)
TOROLAR 40 (40 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TOROLAR 5 5 mg film-coated tablets
Each film-coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).

TOROLAR 10 10 mg film-coated tablets
Each film-coated tablet contains 10 mg rosuvastatin (as rosuvastatin calcium).

TOROLAR 20 20 mg film-coated tablets
Each film-coated tablet contains 20 mg rosuvastatin (as rosuvastatin calcium).

TOROLAR 40 40 mg film-coated tablets
Each film-coated tablet contains 40 mg rosuvastatin (as rosuvastatin calcium).

Excipients with known effect
Each 5 mg film-coated tablet contains 100,915 mg lactose monohydrate.
Each 10 mg film-coated tablet contains 95,706 mg lactose monohydrate.
Each 20 mg film-coated tablet contains 191,412 mg lactose monohydrate.
Each 40 mg film-coated tablet contains 172,824 mg lactose monohydrate.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

TOROLAR 5 5 mg film-coated tablets
Yellow, round, biconvex coated tablet debossed with "ROS" over "5" on one side, plain on the other side.

TOROLAR 10 10 mg film-coated tablets
Pink, round, biconvex, coated tablet debossed with "ROS" over "10" on one side, plain on the other side.

TOROLAR 20 20 mg film-coated tablets
Pink, round, biconvex, coated tablet debossed with "ROS" over "20" on one side, plain on the other side.

TOROLAR 40 40 mg film-coated tablets
Pink, oval, biconvex, coated tablet debossed with "ROS" on one side and "40" on the 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-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, TOROLAR is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:
TOROLAR 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.
TOROLAR is indicated to treat patients with primary dysbetalipoproteinaemia (Fredrickson Type III hyperlipoproteinaemia).
TOROLAR 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).
TOROLAR 40 mg should only be considered in patients with severe hypercholesterolaemia and high cardiovascular risk who do not achieve their treatment goal on 20 mg of TOROLAR or alternative therapy.
Specialist supervision is recommended when the 40 mg dose is initiated. (see section 4.4)

Children and adolescents 10 to 17 years of age:
TOROLAR is indicated to reduce the Total Cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

4.2 Posology and method of administration

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

Posology
The dosage range for TOROLAR is 5 - 40 mg orally once a day. The recommended start dose is 5 mg once a day.
The dose should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the 10 mg dose. However, if necessary, dose adjustment can be made at 2 – 4 week intervals.

Adults:
Primary hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia, dysbetalipoproteinaemia (Frederickson Type III hyperlipoproteinaemia), and isolated hypertriglyceridaemia:
The recommended starting dose is 5 mg once a day.
A 5 mg starting dose is recommended for patients of Asian ancestry and for patients requiring a smaller reduction in LDL-C to achieve treatment target.
For patients with severe hypercholesterolaemia (including heterozygous familial hypercholesterolaemia), a starting dose of 20 mg may be considered.
Homozygous familial hypercholesterolaemia:
For patients with homozygous familial hypercholesterolaemia a starting dose of 20 mg once a day is recommended.
Special populations:

Use in the elderly:
The usual dose range applies.

Dosage in patients with renal insufficiency:
The starting dose applies in patients with mild to moderate renal impairment.
For patients with severe renal impairment the dose of TOROLAR 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 TOROLAR 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above TOROLAR 10 mg should be carefully considered (see section 5.2).

Race:
A 5 mg starting dose of TOROLAR 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:
TOROLAR 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.
TOROLAR 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 commitment rosuvastatin and ciclosporin. For the TOROLAR dose range (10 - 40 mg) this combination is not recommended (see section 4.3).

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

Paediatric population

Children and adolescents 10 - 17 years of age:
In children and adolescents with heterozygous familial hypercholesterolaemia the usual dose range is 5 - 20 mg orally once daily. The dose should be approximately titrated to achieve treatment goal. Safety and efficacy of doses greater than 20 mg have not been studied in this population.
In children and adolescents with homozygous familial hypercholesterolaemia experience is limited to a small number of patients (aged 8 years and above).

Method of administration
TOROLAR may be given at any time of day, with or without food.

4.3 Contraindications

TOROLAR is contraindicated:
- in patients with hypersensitivity to rosuvastatin or to any of the excipients of TOROLAR.
- 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 rosuvastatin, in particular 40 mg, it was transient or intermittent in most cases. Proteinuria has not been shown to be a precursor to acute or progressive renal disease (see section 4.8).
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. TOROLAR 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.
TOROLAR 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 – 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 TOROLAR, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include:
- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- above 70 years of age
- situations where an increase in plasma levels may occur (see sections 4.2, 4.5 and 5.2)
- concomitant use of fibrates.

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

During treatment
Patients must be advised to report inexplicable muscle pain, weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients. Therapy must be discontinued if CK levels are markedly elevated (> 5 x ULN) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are ≤ 5 x ULN).
If symptoms resolve and CK levels return to normal, then consideration should be given to re-introducing TOROLAR 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 TOROLAR. Therefore, the combination of TOROLAR and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of TOROLAR 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
TOROLAR 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 TOROLAR and fusidic acid should only be considered on a case by case basis and under close medical supervision.
TOROLAR 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 TOROLAR, 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. TOROLAR 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 TOROLAR.

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

Protease inhibitors
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 TOROLAR in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating TOROLAR doses in patients treated with protease inhibitors.
The concomitant use with certain protease inhibitors is not recommended unless the dose of TOROLAR 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, TOROLAR 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.
TOROLAR should be used with care in patients with Type 2 diabetes and in patients at risk, being patients with a fasting glucose of 5.6 to 6.9 mmol/l, BMI > 30 kg/m², raised triglycerides or hypertension. Patients at risk must be clinically and biochemically monitored.

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 specific warnings and special precautions for use in adults also apply to children and adolescents.

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

4.5 Interaction with other medicines and other forms of interaction

Effect of co-administered medicines on TOROLAR

Transporter protein inhibitors:
Rosuvastatin, as contained in TOROLAR, 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 TOROLAR 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). TOROLAR 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 TOROLAR and some protease inhibitor combinations may be considered after careful consideration of TOROLAR 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 medicines:
Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin C_{max} and AUC (see section 4.4).
No pharmacokinetic relevant interaction with fenofibrate has been reported, however, a pharmacodynamic interaction may occur. Gemfibrozil, fenofibrate, other fibrates and lipid lowering doses (≥ or equal to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors such as rosuvastatin contained in TOROLAR, 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 TOROLAR and ezetimibe cannot be ruled out (see section 4.4).

Antacid:
The simultaneous dosing of rosuvastatin with an antacid suspension containing aluminium and magnesium hydroxide resulted in a decrease in rosuvastatin plasma concentration of approximately 50 %. This effect was mitigated when the antacid was dosed 2 hours after 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 (see also Table 1 below):
When it is necessary to co-administer TOROLAR with other medicines known to increase exposure to rosuvastatin, doses of TOROLAR should be adjusted.
Start with a 5 mg once daily dose of TOROLAR if the expected increase in exposure (AUC) is approximately 2-fold or higher.
The maximum daily dose of TOROLAR should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of TOROLAR 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 medicinal products on rosuvastatin exposure (AUC; in order of decreasing magnitude) from published clinical trials

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 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 OD, 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 BID, 17 days	20 mg OD, 7 days	2.1-fold ↑
Clopidogrel 300 mg loading, followed by 75 mg at 24 hours	20 mg, single dose	2-fold ↑
Gemfibrozil 600 mg BID, 7 days	80 mg, single dose	1.9-fold ↑
Eltrombopag 75 mg OD, 10 days	10 mg, single dose	1.6-fold ↑
Darunavir 600 mg/ritonavir 100 mg BID, 7 days	10 mg OD, 7 days	1.5-fold ↑
Tipranavir 500 mg/ritonavir 200 mg BID, 11 days	10 mg, single dose	1.4-fold ↑
Dronedarone 400 mg BID	Not available	1.4-fold ↑
Itraconazole 200 mg OD, 5 days	10 mg, single dose	1.4-fold ↑**
Ezetimibe 10 mg OD, 14 days	10 mg, OD, 14 days	1.2-fold ↑**
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 days	10 mg, single dose	↔
Aleglitazar 0.3 mg, 7 days	40 mg, 7 days	↔
Silymarin 140 mg TID, 5 days	10 mg, single dose	↔
Fenofibrate 67 mg TID, 7 days	10 mg, 7 days	↔
Rifampin 450 mg OD, 7 days	20 mg, single dose	↔
Ketoconazole 200 mg BID, 7 days	80 mg, single dose	↔
Fluconazole 200 mg OD, 11 days	80 mg, single dose	↔
Erythromycin 500 mg QID, 7 days	80 mg, single dose	28% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓

*Data given as x-fold change represent a simple ratio between co-administration and rosuvastatin alone. Data given as % change represent % difference relative to rosuvastatin alone.
Increase is indicated as "↑", no change as "↔", decrease as "↓".
**Several interaction studies have been performed at different rosuvastatin dosages, the table shows the most significant ratio
OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily

Effect of TOROLAR on co-administered medicinal products:

Warfarin:
The pharmacokinetics of warfarin is not significantly affected following co-administration with rosuvastatin. However, as with other HMG-CoA reductase inhibitors, co-administration of TOROLAR 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 TOROLAR 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, TOROLAR 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 child-bearing potential should use appropriate contraceptive measures.

Pregnancy
TOROLAR is contraindicated in pregnancy.

Lactation
TOROLAR 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

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

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Thrombocytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions including angioedema
Endocrine disorders	Frequent	Diabetes mellitus†
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache Dizziness
	Less frequent	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
Hepato-biliary disorders	Less frequent	Increased hepatic transaminases Jaundice Hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Pruritis 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 21ecrolizing myopathy
Renal and urinary disorders	Less frequent	Haematuria
	Frequency unknown	Proteinuria
Reproductive system and breast disorders	Less frequent	Gynaecomastia
General disorders and administration site conditions	Frequent	Asthenia
	Less Frequent	Oedema

† Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5.6 mmol/L, BMI > 30 kg/m², raised triglycerides, history of hypertension).
As with other HMG-CoA reductase inhibitors, the incidence of adverse reactions tends to be dose dependent.

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 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 TOROLAR; the majority of cases were mild, asymptomatic and transient.
The following adverse events have been reported with some statins:
- Sexual dysfunction
- Exceptional cases of interstitial lung disease, especially with long term therapy (see section 4.4).

The reporting rates for rhabdomyolysis, serious renal events and serious hepatic events (consisting mainly of increased hepatic transaminases) is higher at the 40 mg dose.

Children and adolescents 10 – 17 years of age
Creatine kinase elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity were observed more frequently in a 52-week clinical trial of children and adolescents compared to adults (see section 4.4).
In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.

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

4.9 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit (see section 5.2).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10AA07.
A 7.5 Serum-cholesterol reducers

Mechanism of action
Rosuvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, the rate-limiting enzyme that converts 3- hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.
Rosuvastatin produces its lipid-modifying effects in 2 ways; it increases the number of hepatic low density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very low density lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.
High density lipoprotein (HDL), which contains apolipoprotein A-I (ApoA-I) is involved, amongst other things, in transport of cholesterol from tissues back to liver (reverse cholesterol transport).
Rosuvastatin reduces elevated LDL-cholesterol (LDL-C), total cholesterol and triglycerides (TG) and increases HDL-cholesterol (HDL-C). It also lowers apolipoprotein B (ApoB) non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I. Rosuvastatin also lowers the LDL-C/HDLC, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.
A therapeutic response to rosuvastatin is evident within 1 week of commencing therapy and 90 % of maximum response is usually achieved by 2 weeks and is maintained after that.

Pharmacodynamic effects
Rosuvastatin reduces or lowers total cholesterol, elevated LDL-cholesterol, triglycerides, ApoB, nonHDL-C, VLDL-C, VLDL-TG. It also lowers the LDL-C/HDL-C, total C/HDL-C and nonHDL-C/HDL-C and the ApoB/ApoA-I ratios.
Rosuvastatin increases HDL-cholesterol and ApoA-I.
Following treatment initiation a therapeutic effect is obtained within 1 week. A 90 % of maximum response is achieved in 2 weeks and is usually achieved by 4 weeks and maintained after that.

Pharmacokinetic properties

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

Distribution
Approximately 90 % of rosuvastatin is bound to plasma proteins, mainly to albumin. The parent compound accounts for greater than 90 % of the circulating active HMG-CoA reductase inhibitor activity.

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

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

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

Special populations

Age and sex
There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin. The pharmacokinetics of rosuvastatin in children and adolescents with heterozygous familial hypercholesterolaemia was similar to that of adult volunteers.

Race
Pharmacokinetic studies show a 1,26 - 2,31 fold elevation in geometric mean AUC (A_{ss}) in Asian subjects compared with Caucasians.
A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) Philipino, 26 (8 %) Korean and 25 (8 %) Vietnamese subjects were evaluated for pharmacokinetic analyses in these studies.
A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics among Caucasian, Hispanic and Black or Afro-Caribbean groups. (see section 4.2, Race).

Renal insufficiency
In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentration of rosuvastatin. However, subjects with severe impairment (CrCl < 30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers. Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

Hepatic insufficiency
In a study with subjects with varying degrees of hepatic impairment, there was no evidence of increased exposure to rosuvastatin in subjects with Child-Pugh scores of 7 or below. However, two subjects with Child- Pugh scores of 8 and 9 showed an increase in systemic exposure of at least 2-fold compared to subjects with lower Child-Pugh scores. There is no experience in subjects with Child-Pugh scores above 9.

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 TOROLAR 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

Colloidal silicon dioxide
Crospovidone
Ferric oxide red or yellow
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Titanium dioxide
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Aluminium/ Aluminium blister
7, 28 and 30 tablets
HDPE container
HDPE bottle for 100 or 500 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.
106 16th Road
Midrand
1686

8 REGISTRATION NUMBER(S)

TOROLAR 5: 48/7.5/0166
TOROLAR 10: 48/7.5/0167
TOROLAR 20: 48/7.5/0168
TOROLAR 40: 48/7.5/0169

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 August 2021

10 DATE OF REVISION OF THE TEXT

19 March 2021

TRLR/PI/A