PROFESSIONAL INFORMATION
SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE
TRINCHOL 5 (5 mg film-coated tablets)
TRINCHOL 10 (10 mg film-coated tablets)
TRINCHOL 20 (20 mg film-coated tablets)
TRINCHOL 40 (40 mg film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
TRINCHOL 5 5 mg film-coated tablets
Each film-coated tablet contains 5 mg rosuvastatin (as rosuvastatin calcium).

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

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

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

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

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

TRINCHOL 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
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, TRINCHOL is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:
TRINCHOL 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.

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

TRINCHOL 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).

TRINCHOL 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 TRINCHOL 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:
TRINCHOL is indicated to reduce the Total Cholesterol, LDL-C and Apo B in patients with heterozygous familial hypercholesterolaemia (HeFH).

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 TRINCHOL 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 (Fredrickson 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 TRINCHOL 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 TRINCHOL 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients, therefore the use of doses above TRINCHOL 10 mg should be carefully considered (see section 5.2).

Race:
A 5 mg starting dose of TRINCHOL 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:
TRINCHOL 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.
TRINCHOL 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 TRINCHOL 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 TRINCHOL 5 mg once daily and should not exceed a dose of TRINCHOL 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
TRINCHOL may be given at any time of day, with or without food.

Contraindications
TRINCHOL is contraindicated:
- in patients with hypersensitivity to rosuvastatin or to any of the excipients of TRINCHOL.
- 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).

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. TRINCHOL 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.
TRINCHOL 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 TRINCHOL, 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 TRINCHOL 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 TRINCHOL. Therefore, the combination of TRINCHOL and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of TRINCHOL 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
TRINCHOL 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 TRINCHOL and fusidic acid should only be considered on a case by case basis and under close medical supervision.
TRINCHOL 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 TRINCHOL, 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. TRINCHOL 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 TRINCHOL.

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 TRINCHOL in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating TRINCHOL doses in patients treated with protease inhibitors.
The concomitant use with certain protease inhibitors is not recommended unless the dose of TRINCHOL 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, TRINCHOL 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.
TRINCHOL 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 special warnings and special precautions for use in adults also apply to children and adolescents.

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

Interaction with other medicines and other forms of interaction
Effect of co-administered medicines on TRINCHOL
Transporter protein inhibitors:
Rosuvastatin, as contained in TRINCHOL, 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 TRINCHOL 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). TRINCHOL 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 TRINCHOL and some protease inhibitor combinations may be considered after careful consideration of TRINCHOL 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 Cmax 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 TRINCHOL, 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 TRINCHOL 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 Cmax 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 TRINCHOL with other medicines known to increase exposure to rosuvastatin, doses of TRINCHOL should be adjusted.
Start with a 5 mg once daily dose of TRINCHOL if the expected increase in exposure (AUC) is approximately 2-fold or higher.
The maximum daily dose of TRINCHOL should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of TRINCHOL 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 TRINCHOL 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 TRINCHOL 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 TRINCHOL 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, TRINCHOL 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.

Fertility, pregnancy and lactation
Women of childbearing potential /Contraception in males and females
Women of child-bearing potential should use appropriate contraceptive measures.
Pregnancy
TRINCHOL is contraindicated in pregnancy.

Lactation
TRINCHOL 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).

Effects on ability to drive and use machines
TRINCHOL may cause dizziness, therefore patients taking TRINCHOL should not drive or use machines until their individual susceptibility to dizziness is known.

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[1]
Psychiatric disorders	Frequency unknown	Depression
Nervous system disorders	Frequent	Headache Dizziness
	Less frequent	Polyneuropathy Memory loss
	Frequency unknown	Peripheral neuropathy
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Cough Dyspnoea
Gastrointestinal disorders	Frequent	Constipation Nausea Abdominal pain
	Less frequent	Pancreatitis
	Frequency unknown	Diarrhoea
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 ecrotizing 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

[1]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 TRINCHOL; 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

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
Pharmacodynamic properties
Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A07.
A 7.5 Serum-cholesterol reducers

Mechanism of action
Rosuvastatin is a selective 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 4 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 $_{(0-t)}$ in Asian subjects compared with Caucasians.
A total of 62 (19 %) Caucasian, 61 (19 %) Chinese, 61 (19 %) Asian-Indian, 35 (11 %) Malay, 27 (8 %) Japanese, 27 (8 %) 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 TRINCHOL 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
List of excipients
Colloidal silicon dioxide
Crospovidone
Ferric oxide red or yellow
Hypromellose
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Titanium dioxide
Triacetin

Incompatibilities
Not applicable.

Shelf life
2 years

Special precautions for storage
This medicinal product does not require any special storage conditions

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.

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)
TRINCHOL 5: 48/7.5/0162
TRINCHOL 10: 48/7.5/0163
TRINCHOL 20: 48/7.5/0164
TRINCHOL 40: 48/7.5/0165

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17 August 2021

10 DATE OF REVISION OF THE TEXT
N.A

TRINITY PHARMA

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PROFESSIONELE INLIGTING
SKEDULERINGSTATUS

S4

1 NAAM VAN DIE MEDISYNE
TRINCHOL 5 (5 mg filmbedekte tablette)
TRINCHOL 10 (10 mg filmbedekte tablette)
TRINCHOL 20 (20 mg filmbedekte tablette)
TRINCHOL 40 (40 mg filmbedekte tablette)

2 KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
TRINCHOL 5 5 mg filmbedekte tablette
Elke filmbedekte tablet bevat 5 mg rosuvastatien (as rosuvastatienkalsium).

TRINCHOL 10 10 mg filmbedekte tablette
Elke filmbedekte tablet bevat 10 mg rosuvastatien (as rosuvastatienkalsium).

TRINCHOL 20 20 mg filmbedekte tablette
Elke filmbedekte tablet bevat 20 mg rosuvastatien (as rosuvastatienkalsium).

TRINCHOL 40 40 mg filmbedekte tablette
Elke filmbedekte tablet bevat 40 mg rosuvastatien (as rosuvastatienkalsium).

Hulpstowwe met bekende effek:
Elke 5 mg filmbedekte tablet bevat 100.915 mg laktose monohidraat.
Elke 10 mg filmbedekte tablet bevat 95.706 mg laktose monohidraat.
Elke 20 mg filmbedekte tablet bevat 191.412 mg laktose monohidraat.
Elke 40 mg filmbedekte tablet bevat 172.824 mg laktose monohidraat.

Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1

3 FARMASEUTIESE VORM
Filmbedekte tablette
TRINCHOL 5 5 mg filmbedekte tablette
Geel, ronde, bikonvekse bedekte tablet gebosseleer met "ROS" oor "5" aan die een kant, plein aan die ander kant.

TRINCHOL 10 10 mg filmbedekte tablette
Pienk, ronde, bikonvekse bedekte tablet gebosseleer met "ROS" oor "10" aan een kant, plein aan die ander kant.

TRINCHOL 20 20 mg filmbedekte tablette
Pienk, ronde, bikonvekse bedekte tablet gebosseleer met "ROS" oor "20" aan een kant, plein aan die ander kant.

TRINCHOL 40 40 mg filmbedekte tablette
Pienk, ovaal, bikonvekse, bedekte tablet gebosseleer met "ROS" aan die een kant en "40" aan die ander kant.

4 KLINIESE BESONDERHEDE
Terapeutiese indikasies

Om die risiko van kardiovaskulêre gebeure te verminder:
By volwasse pasiënte met 'n verhoogde risiko vir aterosklerotiese kardiovaskulêre siektes, gebaseer op die teenwoordigheid van kardiovaskulêre siekte-risikomerkers, soos 'n verhoogde hoë sensitiwiteit C-reaktiewe proteïen (hsCRP) vlak, ouderdom, hipertensie, lae HDL-C, rook of 'n familiegeskiedenis van premature koronêre hartsiektes, word TRINCHOL aangedui om die risiko van nie-fatale beroerte, nie-fatale MI, en die noodsaaklikheid van arteriële revaskularisasie te verminder.

By volwasse pasiënte met hipercholesterolemie:
TRINCHOL is aangedui vir pasiënte met primêre hipercholesterolemie, gemengde dislipidemie en geïsoleerde hipertrigliseriedemie (insluitend Fredrickson Tipe IIa, IIb en IV; en heterosigotiese familiale en nie-familiale hipercholesterolemie) as aanvulling op dieet wanneer respons op dieet en oefening onvoldoende is.

TRINCHOL is aangedui om pasiënte met primêre disbetalipoproteïnemie (Fredrickson Tipe III hiperlipoproteïnemie) te behandel.

TRINCHOL word ook aangedui om die Totale Cholesterol en LDL-C te verminder by pasiënte met homosigotiese familiale hipercholesterolemie, hetsy alleen of as aanvulling tot dieet en ander lipiedverlagende behandelinge (bv. LDL-aferese).

TRINCHOL 40 mg moet slegs oorweeg word by pasiënte met ernstige hipercholesterolemie en 'n hoë kardiovaskulêre risiko wat nie hul behandelingsdoelwit op 20 mg TRINCHOL of alternatiewe terapie bereik nie.

Spesiale toesig word aanbeveel wanneer die dosis van 40 mg geïnisieer word. (sien afdeling 4.4)

Kinders en adolessente 10 tot 17 jarige ouderdom:
TRINCHOL word aangedui om die Totale Cholesterol, LDL-C en Apo B te verminder by pasiënte met heterosigotiese familiale hipercholesterolemie (HeFH).

Posologie en metode van toediening
Voor die aanvang van die behandeling moet die pasiënt op 'n standaard cholesterolverlagende dieet geplaas word wat tydens behandeling voortgesit moet word.
Posologie
Die dosisreeks vir TRINCHOL is 5 - 40 mg oraal een keer per dag. Die aanbevole aanvangsdosis is 5 mg een keer per dag.

Die dosis moet geïndividualiseer word volgens die doel van terapie en die pasiënt se respons. Die meerderheid pasiënte word beheer met die 10 mg dosis. Alhoewel, indien nodig kan dosisaanpassing met 2 - 4 week intervalle gedoen word.

Volwassenes:
Primêre hipercholesterolemie (insluitend heterosigotiese familiale hipercholesterolemie), gemengde dislipidemie, disbetalipoproteïnemie (Fredrickson Tipe III hiperlipoproteïnemie) en geïsoleerde hipertrigliseriedemie:
Die aanbevole aanvangsdosis is 5 mg een keer per dag.
'n Aanvangsdosis van 5 mg word aanbeveel vir pasiënte van Asiatiese voorgeslag en vir pasiënte wat 'n kleiner vermindering in LDL-C benodig om die behandelingsdoelwit te bereik.
Vir pasiënte met ernstige hipercholesterolemie (insluitend heterosigotiese familiale hipercholesterolemie) kan 'n aanvangsdosis van 20 mg oorweeg word.

Homosigotiese familiale hipercholesterolemie:
Vir pasiënte met homosigotiese familiale hipercholesterolemie word 'n aanvangsdosis van 20 mg een keer per dag voorgestel.

Spesiale pasiëntgroepe:
Gebruik in bejaardes:
Die normale dosisreeks is van toepassing.

Dosis by pasiënte met renale ontoereikendheid:
Die aanvangsdosis is van toepassing op pasiënte met ligte tot matige renale inkorting.
Vir pasiënte met ernstige renale inkorting moet die dosis TRINCHOL nie 10 mg een keer per dag oorskry nie.

Dosis by pasiënt met hepatiese ontoereikendheid:
Die normale aanvangsdosis is van toepassing op pasiënte met ligte tot matige hepatiese inkorting. Pasiënte met ernstige hepatiese inkorting moet terapie met TRINCHOL 5 mg begin. Verhoogde sistemiese blootstelling aan rosuvastatien is by hierdie pasiënte waargeneem, daarom moet die gebruik van dosisse bo TRINCHOL 10 mg deeglik oorweeg word (sien afdeling 5.2).

Ras:
'n Aanvangsdosis van 5 mg TRINCHOL moet vir Asiatiese pasiënte oorweeg word. Verhoogde plasmakonsentrasie van rosuvastatien word by Asiatiese proefpersone gesien (sien afdelings 4.4 en 5.2). Die verhoogde sistemiese blootstelling moet in ag geneem word by die behandeling van Asiatiese pasiënte wie se hipercholesterolemie nie voldoende beheer word met dosisse tot 20 mg daagliks nie.

Gelyktydige behandeling:
TRINCHOL het additiewe doeltreffendheid getoon in die verlaging van trigliseriede wanneer dit gebruik word in kombinasie met fenofibraat en die toenemende HDL-C vlakke wanneer dit in kombinasie met niasien gebruik word.
TRINCHOL kan ook gebruik word in kombinasie met esetimieb of galsuursekwestrante (sien afdeling 4.4).

Interaksies wat dosisaanpassings vereis:
Siklosporien:
Verhoogde sistemiese blootstelling aan rosuvastatien is waargeneem by pasiënte wat rosuvastatien en siklosporien gesamentlik neem. Vir die TRINCHOL dosisreeks (10 - 40 mg) word hierdie kombinasie nie aanbeveel nie (sien afdeling 4.3).

Gemfibrosil:
Verhoogde sistemiese blootstelling aan rosuvastatien was waargeneem by proefpersone wat rosuvastatien en gemfibrosil gesamentlik geneem het. Pasiënte wat hierdie kombinasie neem, moet terapie begin met TRINCHOL 5 mg een keer per dag en moet nie 'n dosis van TRINCHOL 20 mg een keer per dag oorskry nie (sien afdeling 4.5).

Pediatriese bevolking
Kinders en adolessente 10 - 17 jarige ouderdom:
By kinders en adolessente met heterosigotiese familiale hipercholesterolemie is die normale dosisreeks 5 – 20 mg oraal een keer per dag. Die dosis moet by benadering getitreer word om die behandelingsdoelwit te bereik. Veiligheid en effektiwiteit van dosisse meer as 20 mg is nie in hierdie populasie bestudeer nie.
By kinders en adolessente met homosigotiese familiale hipercholesterolemie is die ervaring beperk tot 'n klein aantal pasiënte (ouderdom van 8 jaar en ouer).

Metode van toediening
TRINCHOL kan ter enige tyd van die dag gegee word, met of sonder voedsel.

Kontraïndikasies
TRINCHOL is gekontraïndikeerd:
- by pasiënte met hipersensitiwiteit vir rosuvastatien of vir enige van die hulpstowwe van TRINCHOL.
- by pasiënte met aktiewe lewersiekte, insluitend onverklaarbare, aanhoudende verhoging van serumtransaminase en enige serumtransaminase verhogings van meer as 3 keer die boonste limiet van normaal (BLN).
- by pasiënte met erge renale inkorting (kreatienopruiming < 30 ml/min).
- by pasiënte wat gelyktydig siklosporien ontvang (sien afdeling 4.5).
- tydens swangerskap en laktasie en in vroue van kinderbarende potensiaal wat nie voldoende kontraseptiewe maatreëls toepas nie (sien afdeling 4.6).
- by pasiënte met miopatie.
- Die 40 mg dosis is gekontraïndikeerd by pasiënte met predisponerende faktore vir miopatie/rabdomioliese. Sulke faktore sluit in:
  - matige renale inkorting (kreatinienopruiming < 60 ml/min)
  - hipotiroïdisme
  - persoonlike of familiegeskiedenis van oorerflike spierafwykings
  - vorige geskiedenis van spiertoksisiteit met 'n ander HMG-KoA reduktase inhibeerder of fibraat
  - alkohol misbruik
  - situasies waar 'n toename in rosuvastatien-plasmavlakke kan voorkom
  - Asiatiese pasiënte
  - gelyktydige gebruik van fibrate (sien afdelings 4.4, 4.5 en 5.2).

Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Renale Effekte
Proteïnurie, bepaal deur peilstoktoetsing en meestal van tubulêr oorsprong, was waargeneem by pasiënte wat behandel was met hoër dosisse rosuvastatien, veral 40 mg, dit was kortstondig of onderbroke in die meeste gevalle. Daar is nie bewys dat proteïnurie 'n voorloper vir akute of progressiewe renale siekte is nie (sien afdeling 4.8).
Die verslagdoeningskoers vir ernstige renale gebeurtenisse na-bemarkingsgebruik is hoër by die 40 mg dosis. 'n Evaluering van die renale funksie moet oorweeg word tydens die roetine opvolg van pasiënte wat behandel word met 'n dosis van 40 mg.

Skeletspier effekte
Effekte op skeletspier bv. mialgie, miopatie en selde rabdomioliese is aangemeld by pasiënte vir alle dosisse, veral in dosisse hoër as 20 mg.
Soos met ander HMG-KoA reduktase inhibeerders, is die verslagdoeningskoers vir rabdomioliese in na-bemarkingsgebruik hoër by die hoogste bemarkte dosis. Pasiënte wat tekens of simptome ontwikkel wat aandui op miopatie, moet hul kreatinienkinase (KK) vlakke laat meet. TRINCHOL terapie moet gestaak word indien miopatie gediagnoseer of vermoed word.
'n Toename in die voorkoms van miositis en miopatie was opgemerk by pasiënte wat ander HMG-KoA reduktase inhibeerders ontvang, tesame met siklosporien, veselsuurderivate, insluitend gemfibrosil, nikotiensuur, asool-antifungale en makroliedantibiotika.
TRINCHOL moet met omsigtigheid voorgeskryf word by pasiënte met predisponerende faktore vir miopatie, soos renale inkorting, gevorderde ouderdom en hipotiroïdisme, of situasies waar 'n toename in plasmavlakke kan voorkom (sien afdeling 5.2).

Kreatienkinase Metings
Kreatienkinase (KK) moet nie gemeet word na inspannende oefening nie of in die teenwoordigheid van alternatiewe oorsake van toename in KK, wat die interpretasie van die resultaat kan beïnvloed nie. As KK vlakke beduidend verhoog is teen basislyn (> 5 x BLN), moet 'n bevestigingstoets binne 5 - 7 dae uitgevoer word. Indien die herhalingstoets 'n basislyn KK > 5 x **B**LN bevestig, moet die behandeling nie begin word nie

Voor Behandeling
HMG-KoA reduktase inhibeerders, soos TRINCHOL, moet met omsigtigheid voorgeskryf word by pasiënte met predisponerende faktore vir miopatie/rabdomioliese. Sulke faktore sluit in:
- renale inkorting
- hipotiroïdisme
- persoonlike of familiegeskiedenis van oorerflike spierafwykings.
- vorige geskiedenis van spiertoksisiteit met 'n ander HMG-KoA reduktase inhibeerder of fibraat
- alkohol misbruik
- bo 70 jarige ouderdom
- situasies waar 'n toename in plasmavlakke kan voorkom (sien afdeling 4.2, 4.5 en 5.2)
- gelyktydige gebruik van fibrate.

In hierdie pasiëntgroep moet die risiko van behandeling oorweeg word ten opsigte van moontlike voordele. Kliniese monitering word aanbeveel. As KK vlakke beduidend verhoog is teen basislyn (> 5 x **B**LN), moet die behandeling nie geïnisieer word nie.

Tydens behandeling
Pasiënte moet aangeraai word om onverklaarbare spierpyn, swakheid of krampe onmiddellik aan te meld, veral as dit verband hou met malaise of koors. KK vlakke moet by hierdie pasiënte gemeet word. Die behandeling moet gestaak word indien die KK vlakke aansienlik verhoog is (> 5 x **B**LN) of as spiersimptome ernstig is en daaglikse ongemak veroorsaak (selfs al is die KK vlakke ≤ 5 x **B**LN).
Indien simptome oplos en die KK vlakke weer na normaal terugkeer, moet daar oorweeg word om TRINCHOL of 'n alternatiewe HMG-KoA reduktase inhibeerder teen die laagste dosis met noue monitering weer in te stel. Roetine monitering van KK vlakke by asimptomatiese pasiënte is nie geregverdig nie.
Daar is al berig oor 'n immuun-gemedieerde nekrotiserende miopatie (IMNM) tydens of na behandeling met statiene, insluitend rosuvastatien. IMNM word klinies gekenmerk deur proksimale spierswakheid en verhoogde serum kreatienkinase, wat voortduur ondanks die staking van statienbehandeling.
'n Toename in die voorkoms van miositis en miopatie was waargeneem by pasiënte wat ander HMG-KoA reduktase inhibeerders ontvang, tesame met veselsuurderivate, insluitend gemfibrosil, siklosporien, nikotiensuur, asool-antifungale, protease inhibeerders en makroliedantibiotika.

Gemfibrosil
Gemfibrosil verhoog die risiko van miopatie wanneer dit gelyktydig met sommige HMG-KoA reduktase inhibeerders, soos TRINCHOL, gegee word. Daarom word die kombinasie van TRINCHOL en gemfibrosil nie aanbeveel nie. Die voordeel van verdere veranderinge in lipiedvlakke deur die gekombineerde gebruik van TRINCHOL met fibrate of niasien moet noukeurig opgeweeg word ten opsigte van die moontlike risiko's van sulke kombinasies.
Die 40 mg dosis is gekontraïndikeerd met die gesamentlike gebruik van 'n fibraat (sien afdelings 4.5 en 4.8).

Fusidiensuur
TRINCHOL mag nie saam met sistemiese formulerings van fusidiensuur toegedien word nie, of binne 7 dae na staking van fusidiensuur behandeling nie. By pasiënte waar die gebruik van sistemiese fusidiensuur as noodsaaklik beskou word, moet statienbehandeling gestaak word gedurende die duur van fusidiensuur behandeling. Daar was al verslae van rabdomioliese (insluitend 'n paar sterftes) by pasiënte wat fusidiensuur en statiene in kombinasie ontvang het (sien afdeling 4.5).
Pasiënte moet aangeraai word om onmiddellik mediese hulp in te win as hulle simptome van spierswakheid, pyn of teerheid ervaar. Statienterapie kan sewe dae na die laaste dosis fusidiensuur weer ingestel word.
In buitengewone omstandighede, waar langdurige sistemiese fusidiensuur nodig is, bv. vir die behandeling van ernstige infeksies, moet die behoefte aan gelyktydige toediening van TRINCHOL en fusidiensuur slegs van geval tot geval en onder noukeurige mediese toesig oorweeg word.
TRINCHOL moet nie gebruik word by pasiënte met akute, ernstige toestande wat dui op miopatie of wat gepredisponeer is tot die ontwikkeling van renale versaking sekondêr tot rabdomioliese nie (bv. sepsis, hipotensie, groot operasies, trauma, ernstige metaboliese-, endokriene- en elektroliet-versteurings; of onbeheerde stuiptrekking).

Lewer Effekte
HMG-KoA reduktase inhibeerders, soos TRINCHOL, moet met omsigtigheid gebruik word by pasiënte wat oormatige hoeveelhede alkohol verbruik en/of 'n geskiedenis van lewersiekte het.
Dit word aanbeveel dat lewerfunksietoetse uitgevoer word voor en drie maande na die aanvang van die behandeling. TRINCHOL moet gestaak word of die dosis verminder word indien die vlak van serumtransaminase hoër is as 3 keer die boonste limiet van normaal.
Die verslagdoeningskoers vir ernstige hepatiese gebeurtenisse (wat hoofsaaklik bestaan uit verhoogde hepatiese transaminase) in na-bemarkingsgebruik is hoër by die 40 mg dosis.
By pasiënte met sekondêre hipercholesterolemie, wat veroorsaak word deur hipotiroïdisme of nefrotiese sindroom, moet die onderliggende siekte behandel word voor die inisiëring van terapie met TRINCHOL.

Ras
Farmakokinetiese studies toon 'n toename in blootstelling in Asiatiese proefpersone in vergelyking met Kaukasiese proefpersone (sien afdelings 4.2, 4.3 en 5.2).

Protease inhibeerders
Verhoogde sistemiese blootstelling aan rosuvastatien is waargeneem by proefpersone wat rosuvastatien ontvang tesame met verskillende protease inhibeerders in kombinasie met ritonavir.
Die voordeel van lipiedverlaging deur die gebruik van TRINCHOL by MIV pasiënte wat protease inhibeerders ontvang, moet oorweeg word, sowel as die moontlikheid van verhoogde rosuvastatien plasmakonsentrasies by die inisiëring en die op-titrasie van TRINCHOL dosisse by pasiënte wat met protease inhibeerders behandel word.
Die gelyktydige gebruik met sekere protease inhibeerders word nie aanbeveel nie, tensy die TRINCHOL dosis aangepas word (sien afdelings 4.2 en 4.5).

Interstisiële longsiekte
Gevalle van interstisiële longsiekte was aangemeld by sommige statiene, veral met langtermynterapie (sien afdeling 4.8). Presentasie kenmerke kan insluit dispnee, nie-produktiewe hoes en agteruitgang in die algemene gesondheid (moegheid, gewigsverlies en koors). Indien daar vermoed word dat 'n pasiënt interstisiële longsiekte ontwikkel het, moet TRINCHOL gestaak word.

Diabetes Mellitus
Statiene as 'n klas medisyne kan bloedglukose verhoog. By sommige pasiënte, met 'n hoë risiko vir toekomstige diabetes, kan dit 'n vlak van hiperglisemie veroorsaak waar formele diabetiese versorging toepaslik is. Hierdie risiko word egter oorskadu deur die vermindering in vaskulêre risiko met statiene en moet dus nie 'n rede wees om die statienbehandeling te staak nie.
TRINCHOL moet met omsigtigheid gebruik word by pasiënte met Tipe 2 diabetes en by pasiënte op risiko, soos pasiënte met 'n vastende glukose van 5.6 tot 6.9 mmol/l, BMI > 30 kg/m2, verhoogde trigliseriede of hipertensie. Pasiënte op risiko moet klinies en biochemies gemonitor word.

Kinders en adolessente 10 – 17 jarige ouderdom
Die veiligheidsprofiel van rosuvastatien is soortgelyk by kinders of adolessente pasiënte en volwassenes, hoewel KK verhogings > 10 x BLN en spiersimptome na oefening of verhoogde fisiese aktiwiteit, wat met voortgesette behandeling oplos het, meer gereeld by kinders en adolessente waargeneem was. Alhoewel, dieselfde spesiale waarskuwings en spesiale voorsorgmaatreëls vir gebruik by volwassenes geld ook vir kinders en adolessente.

Laktose Intoleransie
TRINCHOL bevat laktose. Pasiënte met seldsame oorerflike probleme van galaktose onverdraagsaamheid, die Lapp laktase tekort of glukose-galaktose wanabsorpsie, moet nie hierdie medisyne neem nie.

Interaksie met ander medisyne en ander vorms van interaksie
Effek van gelyktydig toegediende medisyne op TRINCHOL
Vervoerproteïen inhibeerders:
Rosuvastatien, soos bevat in TRINCHOL, is 'n substraat vir sekere vervoerproteïene, insluitend die hepatiese opnamevervoerder organiese-anioonvervoerpolipeptied 1B1 (OAVP1B1) en uitvloeivervoerder-borskanker-weerstandige proteïen (BKWP). Gelyktydige toediening van TRINCHOL met medisyne wat die vervoerproteïene inhibeer, kan lei tot verhoogde rosuvastatien plasmakonsentrasies en 'n verhoogde risiko vir miopatie (sien afdelings 4.2, 4.4 en 4.5 Tabel 1).

Siklosporien:
Tydens gelyktydige behandeling met rosuvastatien en siklosporien was die rosuvastatien AOK waardes gemiddeld 7 keer hoër as wat by gesonde vrywilligers waargeneem was (sien Tabel 1). TRINCHOL is gekontraïndikeerd by pasiënte wat gelyktydig siklosporien ontvang (sien afdeling 4.3). Gelyke toediening het nie die plasmakonsentrasies van siklosporien geaffekteer nie.

Protease inhibeerders:
Verhoogde sistemiese blootstelling aan rosuvastatien is waargeneem by proefpersone in farmakokinetiese studies wat rosuvastatien ontvang het met verskillende protease inhibeerders in kombinasie met ritonavir (sien Tabel 1 hieronder). Hierdie toename in sistemiese blootstelling aan rosuvastatien kan lei tot 'n verhoogde voorkoms van newe-effekte.
Die gesamentlike gebruik van TRINCHOL en sommige protease inhibeerder kombinasies kan oorweeg word na noukeurige oorweging van die TRINCHOL dosisaanpassings, gebaseer op die verwagte toename in rosuvastatien blootstelling (sien afdelings 4.2, 4.4, 4.5 en Tabel 1 hieronder).

Gemfibrosil en ander lipiedverlagende medisyne:
Gelyktydige gebruik van rosuvastatien en gemfibrosil het gelei tot 'n 2-voudige toename in rosuvastatien K_{maks} en AOK (sien afdeling 4.4).
Geen farmakokinetiese relevante interaksie met fenofibraat is gerapporteer nie, maar 'n farmakodinamiese interaksie kan voorkom. Gemfibrosil, fenofibraat, ander fibrate en lipiedverlagende dosisse niasien (nikotiensuur) (> of gelyk aan 1 g/dag) verhoog die risiko vir miopatie wanneer dit gelyktydig met HMG-KoA reduktase inhibeerders soos rosuvastatien bevat in TRINCHOL gegee word, waarskynlik omdat hulle miopatie kan produseer as dit alleen gegee word. Die 40 mg dosis is gekontraïndikeerd vir die gelyktydige gebruik van 'n fibraat (sien afdelings 4.3 en 4.4). Hierdie pasiënte moet met die 5 mg dosis begin.

Esetimieb:
Gelyktydige gebruik van 10 mg rosuvastatien en 10 mg esetimieb het gelei tot 'n 1.2-voudige toename in AOK van rosuvastatien by hipercholesterolemie proefpersone (Tabel 1). 'n Farmakodinamiese interaksie, in terme van newe-effekte, tussen TRINCHOL en esetimieb, kan nie uitgesluit word nie (sien afdeling 4.4).

Teensuurmiddels:
Die gelyktydige dosering van rosuvastatien met 'n teensuurmiddel suspensie wat aluminium en magnesiumhidroksied bevat, het gelei tot 'n afname in die rosuvastatien plasmakonsentrasie van ongeveer 50 %. Hierdie effek was minder toe die teensuurmiddel 2 uur na rosuvastatien gedoseer was. Die kliniese relevansie van hierdie interaksie is nie bestudeer nie.

Eritromisien:
Gelyktydige gebruik van rosuvastatien en eritromisien het gelei tot 'n 20 % afname in AOK en 'n 30 % afname in K_{maks} van rosuvastatien. Hierdie interaksie kan veroorsaak word deur die toename in derm motiliteit wat deur eritromisien veroorsaak word.

Sitochroom P450 ensieme:
In vitro- en *in vivo*-data dui aan dat rosuvastatien geen klinies beduidende sitochroom P450 interaksies het nie (as 'n substraat, inhibeerder of induseerder). Daarom word medisyne-interaksies wat voortspruit uit sitochroom P450 gemedieerde metabolisme nie verwag nie. Geen klinies relevante interaksies was waargeneem tussen rosuvastatien en flukonasool ('n inhibeerder van CYP2C9 en CYP3A4) of ketokonasool ('n inhibeerder van CYP2A6 en CYP3A4) nie.

Interaksies wat rosuvastatien dosisaanpassings vereis (sien ook Tabel 1 hieronder):
Wanneer dit nodig is om TRINCHOL saam met ander medisyne toe te dien wat bekend is dat dit blootstelling aan rosuvastatien verhoog, moet TRINCHOL dosisse aangepas word.
Begin met 'n 5 mg een keer per dag dosis van TRINCHOL as die verwagte toename in blootstelling (AOK) ongeveer 2-voudig of hoër is.
Die maksimum daaglikse dosis TRINCHOL moet aangepas word sodat die verwagte rosuvastatien blootstelling nie die hoeveelheid van 'n 40 mg daaglikse dosis TRINCHOL wat geneem is sonder interaktiewe medisyne oorskry nie, byvoorbeeld 'n 20 mg dosis van rosuvastatien met gemfibrosil (1,9-voudige toename), en 'n 10 mg dosis van rosuvastatien met kombinasie ritonavir/atasanavir (3.1-voudige toename).

Tabel 1. Effek van gelyktydig toegediende medisinale produkte op rosuvastatien blootstelling (AOK; in volgorde van afnemende omvang) uit gepubliseerde kliniese proewe

Interaktiewe medisyne dosisregime	Rosuvastatien dosisregime	Verandering in rosuvastatien AOK*
Siklosporien 75 mg BID tot 200 mg BID, 6 maande	10 mg OD, 10 dae	7.1-voudig
Regorafenib 160 mg, een keer per dag, 14 dae	5 mg, enkel dosis	3.8-voudig ↑
Atasanavir 300 mg/ritonavir 100 mg OD, 8 dae	10 mg, enkel dosis	3.1-voudig
Velpatasvir 100 mg een keer per dag	10 mg, enkel dosis	2.7-voudig ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg een keer per dag / dasabuvir 400 mg twee keer per dag, 14 dae	5 mg, enkel dosis	2.6-voudig ↑
Grasoprevir 200 mg/elbasvir 50 mg een keer per dag, 11 dae	10 mg, enkel dosis	2.3-voudig ↑
Glekaprevir 400 mg/pibrentasvir 120 mg een keer per dag, 7 dae	5 mg een keer per dag, 7 dae	2.2-voudig ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 dae	20 mg OD, 7 dae	2.1-voudig
Klopidogrel 300 mg laai dosis, gevolg deur 75 mg na 24 uur	20 mg, enkel dosis	2-voudig ↑
Gemfibrosil 600 mg BID, 7 dae	80 mg, enkel dosis	1.9-voudig
Eltrombopag 75 mg OD, 10 dae	10 mg, enkel dosis	1.6-voudig
Darunavir 600 mg/ritonavir 100 mg BID, 7 dae	10 mg OD, 7 dae	1.5-voudig
Tipranavir 500 mg/ritonavir 200 mg BID, 11 dae	10 mg, enkel dosis	1.4-voudig
Dronedaroon 400 mg BID	Nie beskikbaar	1.4-voudig
Itrakonasool 200 mg OD, 5 dae	10 mg, enkel dosis	1.4-voudig **
Esetimieb 10 mg OD, 14 dae	10 mg, OD, 14 dae	1.2-voudig **
Fosamprenavir 700 mg/ritonavir 100 mg BID, 8 dae	10 mg, enkel dosis	«
Aleglitasar 0.3 mg, 7 dae	40 mg, 7 dae	«
Silimarin 140 mg TID, 5 dae	10 mg, enkel dosis	«
Fenofibrate 67 mg TID, 7 dae	10 mg, 7 dae	«
Rifampien 450 mg OD, 7 dae	20 mg, enkel dosis	«
Ketokonasool 200 mg BID, 7 dae	80 mg, enkel dosis	«
Flukonasool 200 mg OD, 11 dae	80 mg, enkel dosis	«
Eritromisien 500 mg QID, 7 dae	80 mg, enkel dosis	28 % ‾‾
Baikalien 50 mg TID, 14 dae	20 mg, enkel dosis	47 % ‾‾

*Data gegewe as x-voudige verandering, verteenwoordig 'n eenvoudige verhouding tussen gelyke toediening en rosuvastatien alleen. Data gegewe as % verandering, verteenwoordig % verskil relatief tot rosuvastatien alleen.
Toenames is aangedui as "", geen verandering as "«", dalings as "‾".
**Verskeie interaksiestudies was uitgevoer teen verskillende rosuvastatien dosisse, die tabel vertoon die mees belangrikste verhouding
OD = een keer per dag; BID = twee keer per dag; TID = drie keer per dag; QID = vier keer per dag

Effek van TRINCHOL op gelyktydig toegediende medisinale produkte:
Warfarien:
Die farmakokinetika van warfarien word nie beduidend beïnvloed na gelyktydige toediening van rosuvastatien nie. Alhoewel, soos met ander HMG-KoA reduktase inhibeerders, kan die gelyktydige toediening van TRINCHOL en warfarien lei tot 'n toename in die Internasionale Genormaliseerde Verhouding (IGV) in vergelyking met warfarien alleen. By pasiënte wat warfarien neem, word aanbeveel dat IGV gemonitor word beide, met die aanvang of beëindiging van die behandeling met TRINCHOL óf na dosisaanpassing.

Orale kontrasepsie/hormoonvervangingsterapie (HVT):
Gelyktydige gebruik van rosuvastatien en 'n orale kontrasepsie het gelei tot 'n toename in etinielestradiol en norgestrel AOK van 26 % en 34 % onderskeidelik. Hierdie verhoogde plasmavlakke moet oorweeg word by die keuse van orale kontraseptiewe dosisse. Daar is geen farmakokinetiese data beskikbaar by proefpersone wat gelyktydig rosuvastatien en hormoonvervangingsterapie gebruik nie, daarom kan 'n soortgelyke effek nie uitgesluit word nie.

Ander medisyne:
Digoksien:
Op grond van data uit spesifieke interaksiestudies word geen klinies relevante interaksie met digoksien verwag nie.

Fusidiensuur:
Interaksiestudies met rosuvastatien en fusidiensuur is nie uitgevoer nie. Die risiko van miopatie, insluitend rabdomioliese, kan verhoog word deur die gelyktydige toediening van sistemiese fusidiensuur met statiene. Die meganisme van hierdie interaksie (hetsy dit farmakodinamies of farmakokineties is, of albei) is nog onbekend. Daar is al berig oor rabdomioliese (insluitend 'n paar sterftes) by pasiënte wat hierdie kombinasie ontvang het.
Indien behandeling met sistemiese fusidiensuur noodsaaklik is, moet TRINCHOL behandeling gestaak word gedurende die duur van die behandeling met fusidiensuur (sien afdeling 4.4).

Pediatriese populasie:
Interaksiestudies is slegs by volwassenes uitgevoer. Die omvang van interaksies in die pediatriese populasie is nie bekend nie.

Vrugbaarheid, swangerskap en laktasie
Vroue van kinderbarende potensiaal /Kontrasepsie in mans en vroue
Vroue wat swanger kan raak, moet toepaslike voorbehoedmaatreëls gebruik.

Swangerskap
TRINCHOL is gekontraïndikeerd in swangerskap.

Laktasie
TRINCHOL is gekontraïndikeerd tydens laktasie. Rosuvastatien word in die melk van rotte uitgeskei. Daar is geen data beskikbaar met betrekking tot die uitskeiding van rosuvastatien in melk by mense nie (sien afdeling 4.3).

Uitwerking op die vermoë om te bestuur en masjiene te gebruik
TRINCHOL kan duiseligheid veroorsaak, daarom moet pasiënte wat TRINCHOL neem nie bestuur of masjiene gebruik totdat hul individuele vatbaarheid vir duiseligheid bekend is nie.

Newe-effekte
Getabuleerde opsomming van newe-effekte

MedDRA sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Bloed- en die limfstelselversteurings	Minder gereeld	Trombositopenie
Immuunstelsel versteurings	Minder gereeld	Hipersensitiwiteitsreaksies insluitend angioedeem
Endokriene versteurings	Gereeld	Diabetes mellitus[1]
Psigiatriese versteurings	Frekwensie onbekend	Depressie
Senusisteemversteurings	Gereeld	Hoofpyn Duiseligheid
	Minder gereeld	Polineuropatie Geheueverlies
	Frekwensie onbekend	Perifere neuropatie
Respiratoriese, torakale- en mediastinale versteurings	Frekwensie onbekend	Hoes Dispnee
Gastro-intestinale versteurings	Gereeld	Konstipasie Naarheid Abdominale pyn
	Minder gereeld	Pankreatitis
	Frekwensie onbekend	Diarree
Hepato-biliêre versteurings	Minder gereeld	Verhoogde hepatiese transaminase Geelsug Hepatitis
Vel- en Onderhuidse weefselversteurings	Minder gereeld	Pruritus Uitslag Urtikarie
	Frekwensie onbekend	Stevens-Johnson sindroom
Muskuloskeletale bindweefselversteurings	Gereeld	Mialgie
	Minder gereeld	Miopatie (insluitend miositis) Rabdomioliese Lupusagtige sindroom Skeur van spiere Artralgie
	Frekwensie onbekend	Tendonafwykings, soms vererger deur skeuring Immuunbemiddelde nekrotiserende miopatie
Renale en urinêre versteurings	Minder gereeld	Hematurie
	Frekwensie onbekend	Proteïnurie
Voortplantingstelsel- en borsversteurings	Minder gereeld	Ginekomastie
Algemene versteurings en toedieningsplektoestande	Gereeld	Astenie
	Minder gereeld	Edeem

[1]Frekwensie sal afhang van die teenwoordigheid of afwesigheid van risikofaktore (die vastende bloedglukose ≥ 5,6 mmol/L, BMI > 30 kg/m2, verhoogde trigliseriede, geskiedenis van hipertensie).
Soos met ander HMG-KoA reduktase inhibeerders, is die voorkoms van newe-effekte geneig om dosisafhanklik te wees.

Beskrywing van geselekteerde newe-effekte
Renale effekte:
Proteïnurie, bepaal deur peilstoktoetsing en meestal van tubulêre oorsprong, was waargeneem by pasiënte wat met rosuvastatien behandel was. Veranderinge in urienproteïene van geen of spoor na 100 mg/dL of meer was gesien by < 1 % van die pasiënte een of ander tyd tydens behandeling met 10 en 20 mg, en by ongeveer 3 % van die pasiënte wat met 40 mg behandel was. 'n Geringe toename in die verskuiwing van geen of spoor na 30 mg/dL was waargeneem met die 20 mg dosis. In die meeste gevalle neem proteïnurie af of verdwyn spontaan met voortgesette terapie. Die hersiening van data uit kliniese proewe en na-bemarkingservaring tot op hede het nie 'n oorsaaklike assosiasie tussen proteïnurie en akute of progressiewe renale siekte geïdentifiseer nie.
Hematurie was waargeneem by pasiënte wat met rosuvastatien behandel was, en kliniese proefdata toon dat die voorkoms laag is.

Skeletspier effekte:
Effekte op skeletspier bv. mialgie, miopatie (insluitend miositis) en, selde, rabdomioliese met en sonder akute renale versaking was aangemeld by rosuvastatien behandelde pasiënte met alle dosisse, veral met dosisse > 20 mg.
'n Dosisverwante toename in KK vlakke was waargeneem by pasiënte wat rosuvastatien geneem het; die meerderheid gevalle was lig, asimptomaties en kortstondig. Indien KK vlakke verhoog is (> 5 x BLN), moet die behandeling gestaak word (sien afdeling 4.4).

Lewer effekte:
'n Dosisverwante toename in transaminase was waargeneem by 'n klein aantal pasiënte wat rosuvastatien geneem het soos in TRINCHOL; die meerderheid van die gevalle was lig, asimptomaties en kortstondig.
Die volgende newe-effekte was by sommige statiene aangemeld:
- Seksuele disfunksie.
- Uitsonderlike gevalle van interstisiële longsiekte, veral met langtermynterapie (sien afdeling 4.4).

Die verslagdoeningskoers vir rabdomioliese, ernstige renale gebeurtenisse en ernstige hepatiese gebeurtenisse (wat hoofsaaklik bestaan uit verhoogde hepatiese transaminase) is hoër by die 40 mg dosis.

Kinders en adolessente 10 – 17 jarige ouderdom
Kreatienkinase verhogings > 10 x BLN en spiersimptome na oefening óf verhoogde fisiese aktiwiteit was meer gereeld waargeneem in 'n 52-week kliniese proef by kinders en adolessente in vergelyking met volwassenes (sien afdeling 4.4).
In ander opsigte was die veiligheidsprofiel van rosuvastatien soortgelyk by kinders en adolessente in vergelyking met volwassenes.

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "**6.04 Adverse Drug Reactions Reporting Form**", wat aanlyn by SAHPRA se publikasies gevind kan word:
https://www.sahpra.org.za/Publications/Index/8

Oordosering
Daar is geen spesifieke behandeling in geval van oordosering nie. In geval van oordosering, moet die pasiënt simptomaties behandel word, en ondersteunende maatreëls ingestel word soos benodig. Lewerfunksie en KK vlakke moet gemonitor word. Dit is onwaarskynlik dat hemodialise voordelig sal wees (sien afdeling 5.2).

5 FARMAKOLOGIESE EIENSKAPPE
Farmakodinamiese eienskappe
Farmakoterapeutiese groep: HMG-KoA reduktase inhibeerders, ATC kode: C10A A07.
A 7.5 Serum-cholesterol verlagers

Meganisme van werking
Rosuvastatien is 'n selektiewe en mededingende inhibeerder van 3-hidroksi-3-methiel-glutariel-KoA (HMG-KoA) reduktase, die tempo-beperkende ensiem wat 3-hydroxi-3-methiel-glutariel koënsiem A omskakel na mevalonaat, 'n voorloper vir cholesterol. Die primêre werkingsplek van rosuvastatien is in die lewer, die teikenorgaan vir cholesterolverlaging.
Rosuvastatien lewer sy lipied-modifiserende effekte op 2 maniere; dit verhoog die aantal hepatiese lae digtheid lipoproteïen (LDL) reseptore op die seloppervlakte, wat die van opname en katabolisme van LDL verbeter én dit inhibeer die hepatiese sintese van baie lae digtheid lipoproteïen (VLDL) wat die totale aantal VLDL- en LDL-deeltjies sodoende verminder.
Hoëdigtheid lipoproteïen (HDL), wat apolipoproteïen A-I (ApoA-I) bevat, is onder meer betrokke by die vervoer van cholesterol vanaf weefsels terug na die lewer toe (omgekeerde cholesterolvervoer).
Rosuvastatien verminder verhoogde LDL-cholesterol (LDL-C), totale cholesterol en trigliseriede (TG) en verhoog HDL-cholesterol (HDL-C). Dit verlaag ook apolipoproteïen B (ApoB) nie-HDL-C, VLDL-C, VLDL-TG en verhoog ApoA-I. Rosuvastatien verlaag ook die LDL-C/HDLC, totale C/HDL-C en nie-HDL-C/HDL-C en die ApoB/ApoA-I verhoudings.
'n Terapeutiese respons op rosuvastatien is duidelik binne 1 week na die aanvang van die behandeling, en 90 % van die maksimum respons word gewoonlik bereik teen 4 weke en word daarna gehandhaaf.

Farmakodinamiese effekte
Rosuvastatien verminder of verlaag totale cholesterol, verhoogde LDL-cholesterol, trigliseriede, ApoB, nie-HDL-C, VLDL-C, VLDL-TG. Dit verlaag ook die LDL-C/HDL-C, totale C/HDL-C en nie-HDL-C/HDL-C en die ApoB/ApoA-I verhoudings.
Rosuvastatien verhoog HDL-cholesterol en ApoA-I.
Na die inisiasie van die behandeling word 'n terapeutiese effek binne 1 week verkry. 'n 90 % Maksimum respons word gewoonlik bereik teen 4 weke en gehandhaaf daarna.

Farmakokinetiese eienskappe
Absorpsie
Maksimum rosuvastatien plasmakonsentrasies word ongeveer 5 uur na orale toediening bereik. Die absolute biobeskikbaarheid is ongeveer 20 %.

Verspreiding
Ongeveer 90 % van rosuvastatien is aan plasmaproteïene gebind, hoofsaaklik aan albumien. Die ouerverbinding maak meer as 90 % van die sirkulerende aktiewe HMG-KoA reduktase inhiberingsaktiwiteit uit.

Biotransformasie
Rosuvastatien ondergaan beperkte metabolisme in mense (ongeveer 10 %) hoofsaaklik na die N-desmetiel vorm.

Eliminasie
Ongeveer 90 % van die rosuvastatien dosis word onveranderd uitgeskei in die feses en die oorblywende deel word uitgeskei in die urien.

Lineariteit/nie-lineariteit
Sistemiese blootstelling aan rosuvastatien neem toe in verhouding tot die dosis. Daar is geen veranderinge in farmakokinetiese parameters na veelvuldige daaglikse dosisse nie.

Spesiale populasies
Ouderdom en geslag
Daar was geen klinies relevante effek van ouderdom of geslag op die farmakokinetika van rosuvastatien nie. Die farmakokinetika van rosuvastatien by kinders en adolessente met heterosigotiese familiale hipercholesterolemie was soortgelyk aan dié van volwasse vrywilligers.

Ras
Farmakokinetiese studies toon 'n 1,26 - 2,31-voudige toename in geometriese gemiddelde AOK$_{(0-t)}$ in Asiatiese proefpersone in vergelyking met Kaukasiërs.
'n Totaal van 62 (19 %) Kaukasiërs, 61 (19 %) Sjinees, 61 (19 %) Asiër-Indiër, 35 (11 %) Maleise, 27 (8 %) Japannees, 27 (8 %) Filippyns, 26 (8 %) Koreaans en 25 (8 %) Viëtnamese proefpersone was geëvalueer vir farmakokinetiese analise in hierdie studies.
'n Populasie-farmakokinetiese analise het geen klinies relevante verskille in farmakokinetika onder Kaukasiese, Spaanse en Swart- of Afro-Karibiese groepe geopenbaar nie. (sien afdeling 4.2, Ras).

Renale inkorting
In 'n studie onder proefpersone met verskillende grade van renale inkorting het ligte tot matige renale siekte min invloed op die plasmakonsentrasie van rosuvastatien gehad. Alhoewel, proefpersone met ernstige inkorting (CrCl < 30 ml/min) het 'n 3-voudige toename in plasmakonsentrasie gehad in vergelyking met gesonde vrywilligers. Dit is onwaarskynlik dat hemodialise tot voordeel sal wees vir die verwydering van rosuvastatien.

Hepatiese inkorting
In 'n studie van proefpersone met verskillende grade van hepatiese inkorting, was daar geen bewyse van verhoogde blootstelling aan rosuvastatien by persone met Child-Pugh tellings van 7 of minder nie. Alhoewel, twee proefpersone met Child-Pugh tellings van 8 en 9 het 'n toename in sistemiese blootstelling van ten minste 2-voudig getoon in vergelyking met proefpersone met 'n laer Child-Pugh telling. Daar is geen ervaring in proefpersone met Child-Pugh tellings bo 9 nie.

Genetiese polimorfismes
Disposisie van HMG-KoA reduktase inhibeerders, insluitend rosuvastatien, betrek OATP1B1 en BCRP-vervoerproteïene. By pasiënte met SLCO1B1 (OATP1B1) en/of ABCG2 (BCRP) genetiese polimorfismes is daar 'n risiko vir verhoogde rosuvastatien blootstelling. Individuele polimorfismes van SLCO1B1 c.521CC en ABCG2 c.421AA hou verband met 'n hoër rosuvastatien blootstelling (AOK) in vergelyking met die SLCO1B1 c.521TT of ABCG2 c.421CC genotipes. Hierdie spesifieke genotipering is nie in die kliniese praktyk vasgestel nie, maar vir pasiënte wat bekend is dat hulle hierdie soort polimorfismes het, word 'n laer daaglikse dosis TRINCHOL aanbeveel.

Pediatriese populasie
Twee farmakokinetiese studies met rosuvastatien (gegee as tablette) by pediatriese pasiënte met heterosigotiese familiale hipercholesterolemie 10 tot 17 of 6 tot 17 jarige ouderdom (totaal van 214 pasiënte) het getoon dat blootstelling by pediatriese pasiënte skynbaar vergelykbaar of laer is as by volwasse pasiënte. Rosuvastatien blootstelling was voorspelbaar ten opsigte van dosis en tyd oor 'n 2 jaar periode.

6 FARMSEUTIESE BESONDERHEDE
Lys van hulpstowwe
Ferrisoksied rooi of geel
Hipromellose
Kolloïdale silikondioksied
Kruispovidoon
Laktose monohidraat
Magnesiumstearaat
Mikrokristallien sellulose
Titanium dioksied
Triasetien

Onverenigbaarheid
Nie van toepassing.

Rakleeftyd
2 jaar

Spesiale voorsorgmaatreëls tydens berging
Hierdie medisinale produk vereis nie enige spesiale bergingstoestande nie

Aard en inhoud van die houer
Aluminium/ Aluminium stolpverpakking
7, 28 en 30 tablette

HDPE houer
HDPE bottel vir 100 of 500 tablette.

Nie alle verpakkingsgroottes mag moontlik bemark word nie.

Spesiale voorsorgmaatreëls vir wegdoening
Geen spesiale vereistes.

7 HOUER VAN REGISTRASIESERTIFIKAAT
Trinity Pharma (Pty) Ltd.
106 16th Weg
Midrand
1686

8 REGISTRASIENOMMER(S)
TRINCHOL 5: 48/7.5/0162
TRINCHOL 10: 48/7.5/0163
TRINCHOL 20: 48/7.5/0164
TRINCHOL 40: 48/7.5/0165

9 DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING
17 Augustus 2021

10 DATUM VAN HERSIENING VAN DIE TEKS
N.A