SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

COLEROS 5 (5 mg film-coated tablets)

COLEROS 10 (10 mg film-coated tablets)

COLEROS 20 (20 mg film-coated tablets)

COLEROS 40 (40 mg film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COLEROS 5: Each film-coated tablet contains rosuvastatin calcium equivalent to 5 mg rosuvastatin.

COLEROS 10: Each film-coated tablet contains rosuvastatin calcium equivalent to 10 mg rosuvastatin.

COLEROS 20: Each film-coated tablet contains rosuvastatin calcium equivalent to 20 mg rosuvastatin.

COLEROS 40: Each film-coated tablet contains rosuvastatin calcium equivalent to 40 mg rosuvastatin.

Excipients with known effect

Each 5 mg film-coated tablet contains 20,775 mg lactose monohydrate.

Each 10 mg film-coated tablet contains 41,550 mg lactose monohydrate.

Each 20 mg film-coated tablet contains 83,100 mg lactose monohydrate.

Each 40 mg film-coated tablet contains 166,200 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

COLEROS 5: Pink, 4,50 mm, round, biconvex, bevelled edge, film-coated tablet, debossed with ‘R5’ on one side and plain on other side

COLEROS 10: Pink, 5,50 mm, round, biconvex, bevelled edge, film-coated tablet, debossed with ‘R10’ on one side and plain on other side.

COLEROS 20: Pink, 7,00 mm, round, biconvex, film-coated tablet, debossed with 'R20' on one side and plain on other side.

COLEROS 40: Pink, 11,50 mm x 6,90 mm, oval, biconvex, film-coated tablet, debossed with 'R40' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To reduce the risk of cardiovascular events:

In adult patients with an increased risk of atherosclerotic cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated high-sensitivity C-reactive protein (hsCRP) level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, COLEROS is indicated to reduce the risk of non-fatal stroke, non-fatal MI, and the need for arterial revascularisation.

In adult patients with hypercholesterolaemia:

COLEROS 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.

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

COLEROS 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).

COLEROS 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 COLEROS 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:

COLEROS 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 is initiated, the patient should be placed on a standard cholesterol-lowering diet that should continue for the duration of treatment.

The dosage range for COLEROS is 5 mg - 40 mg, orally, once a day. The recommended starting dose is 5 mg once daily.

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 may be made at 2 – 4 week intervals.

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

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 daily.

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 goal.

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.

Children and adolescents 10-17 years of age:

In children and adolescents with heterozygous familial hypercholesterolaemia the usual dosage 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).

Special populations:

Use in the elderly:

The usual dosage range applies.

Dosage in patients with renal insufficiency:

The starting dose applies to patients with mild to moderate renal impairment.

For patients with severe renal impairment the dose of COLEROS must not exceed 10 mg once daily.

Dosage in patients with hepatic insufficiency:

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

Race:

A 5 mg starting dose of COLEROS 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 hypercholesterolemia is not adequately controlled at doses up to 20 mg daily.

Concomitant therapy:

COLEROS 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.

COLEROS 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 COLEROS and ciclosporin concomitantly. For the COLEROS dosage range of 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 COLEROS and gemfibrozil. Patients taking this combination should start therapy with COLEROS 5 mg once daily and should not exceed a dose of COLEROS 20 mg once daily (see section 4.5).

4.3 Contraindications

COLEROS is contraindicated:

- in patients with hypersensitivity to rosuvastatin or to any of the excipients of COLEROS listed in section 6.1.
- 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 with myopathy.
- in patients receiving concomitant ciclosporin.
- during pregnancy and lactation and in women of childbearing potential not using appropriate contraceptive measures.

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 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 COLEROS, 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 rhabdomyolysis have been reported in patients at all doses, particularly at doses higher than 20 mg.

Cases of rhabdomyolysis have been reported with the concomitant use of ezetimibe and a HMG-CoA reductase inhibitor, such as COLEROS. A pharmacodynamic interaction cannot be excluded (see section 4.5). Caution should be exercised with their concomitant use.

The reporting rate for rhabdomyolysis, in post-marketing use, is higher at the 40 mg dose.

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 (>5xULN) a confirmatory test should be carried out within 5 – 7 days. If the repeat test confirms a baseline CK >5xULN, treatment must not be started.

Before treatment

HMG-CoA reductase inhibitors, such as COLEROS, 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 (>5xULN) 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 myopathy is diagnosed or suspected.

There have been very rare 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.

Myasthenia gravis and ocular myasthenia

Risk of myasthenia gravis and ocular myasthenia.

Gemfibrozil

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

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

COLEROS 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 COLEROS, 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. COLEROS 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 COLEROS.

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 COLEROS in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating COLEROS doses in patients treated with protease inhibitors.

The concomitant use with certain protease inhibitors is not recommended unless the dose of COLEROS is adjusted (see sections 4.2 and 4.5).

Interstitial Lung Disease

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

Diabetes Mellitus

Satins 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.

COLEROS should be used with care in patients with Type 2 diabetes and in patients at risk, being patients with a fasting glucose of 5.6 to 6.9 mmol/l, BMI >30 kg/m^2, raised triglycerides or hypertension. At risk patients must be clinically and biochemically monitored.

Children and adolescents 10 – 17 years of age

It has been reported that after a two-year study period there was no effect on growth (height), weight, BMI (body mass index) or secondary characteristics of sexual maturation by Tanner staging in paediatric patients 6 to 17 years of age when taking rosuvastatin, as contained in COLEROS (see section 5.1)

There have been reports in children and adolescents receiving rosuvastatin as contained in COLEROS for 52 weeks, that CK elevations > 10 x ULN and muscle symptoms following exercise or increased physical activity were observed more frequently than compared to that reported in adults (see section 4.8).

Lactose Intolerance

Patients with rare hereditary problems of galactose intolerance, total 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 medicinal products on COLEROS

Transporter protein inhibitors:

Rosuvastatin, as contained in COLEROS, is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of COLEROS with medicinal products that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see sections 4.2, 4.4 and 4.5 Table 1).

Ciclosporin:

During concomitant treatment with COLEROS and ciclosporin, rosuvastatin AUC values were on average 7 times higher than those observed in healthy volunteers (see Table 1). COLEROS 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 COLEROS with various protease inhibitors in combination with ritonavir.

The lowest dose of COLEROS that provides therapeutic benefit to the patient should be used, and close monitoring of adverse events is indicated.

Consideration should be given both to the benefit of lipid lowering by the use of COLEROS in HIV-infected patients receiving protease inhibitors and the potential risks of this increased rosuvastatin plasma

concentrations when initiating and up-titrating COLEROS doses in patients treated with protease inhibitors, as the combination may lead to an increased incidence of adverse events (see section 4.4).

Gemfibrozil and other lipid-lowering products:

Concomitant use of COLEROS 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 COLEROS, 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 COLEROS 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 COLEROS and ezetimibe cannot be ruled out (see section 4.4).

Antacid:

The simultaneous dosing of COLEROS 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 COLEROS. The clinical relevance of this interaction has not been studied.

Erythromycin:

Concomitant use of COLEROS 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 COLEROS with other medicinal products known to increase exposure to rosuvastatin, doses of COLEROS should be adjusted.

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

The maximum daily dose of COLEROS should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of COLEROS taken without interacting medicines, for example a 20 mg dose of COLEROS with gemfibrozil (1.9-fold increase), and a 10 mg dose of COLEROS 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, OD, 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 OD	10 mg, single dose	2,7-fold ↑
Ombitasvir 25 mg/paritaprevir 150 mg/ Ritonavir 100 mg OD/ dasabuvir 400 mg BID, 14 days	5 mg, single dose	2,6-fold ↑
Grazoprevir 200 mg/elbasvir 50 mg OD, 11 days	10 mg, single dose	2,3-fold ↑
Glecaprevir 400 mg/pibrentasvir 120 mg OD, 7 days	5 mg OD, 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, 5 days	10 mg, single dose	1,6-fold ↑

Interacting drug dose regimen	Rosuvastatin dose regimen	Change in rosuvastatin AUC*
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	↔
Rifampicin 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	20 % ↓
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 dosages, the table shows the most significant ratio OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.

Effect of rosuvastatin on co-administered medicines

Vitamin K antagonists:

As with other HMG-CoA reductase inhibitors, the initiation of treatment or dosage up-titration of COLEROS in patients treated concomitantly with vitamin K antagonists (e.g. warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR).

Discontinuation or down-titration of COLEROS may result in a decrease in INR. In such situations, appropriate monitoring of INR is recommended.

Oral contraceptive/hormone replacement therapy (HRT):

Concomitant use of COLEROS and an oral contraceptive resulted in an increase in ethinylestradiol 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 COLEROS and HRT, 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, COLEROS treatment should be discontinued throughout the duration of the fusidic acid treatment (see section 4.4).

Paediatric population:

Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use appropriate contraceptive measures.

Pregnancy

COLEROS is contraindicated in pregnancy.

Breastfeeding

COLEROS is contraindicated in lactation.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The adverse reactions seen with COLEROS are generally mild and transient.

Table 2: Tabulated list of adverse reactions:

SOC	Frequency	
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 Sleep disturbances (including insomnia and nightmares) Myasthenia gravis
Eye disorders	*Frequency unknown*	Ocular myasthenia
Respiratory, thoracic and mediastinal disorders	*Frequency unknown*	Cough Dyspnoea
Gastrointestinal disorders	*Frequent*	Constipation Nausea Abdominal pain
	Less frequent	Pancreatitis
	Frequency unknown	Diarrhoea
Hepatobiliary disorders	*Less frequent*	Increased hepatic transaminases Jaundice Hepatitis
Skin and subcutaneous tissue disorders	*Less frequent*	Pruritus Rash Urticaria
	Frequency unknown	Stevens- Johnson syndrome
Musculoskeletal and connective tissue disorders	*Frequent*	Myalgia
	Less frequent	Myopathy (including myositis) Rhabdomyolysis Lupus-like syndrome Muscle rupture Arthralgia
	Frequency unknown	Tendon disorders, sometimes complicated by rupture Immune- mediated necrotising myopathy
Renal and urinary disorders	*Less frequent*	Haematuria
	Frequency unknown	Proteinuria
Reproductive system and breast disorders	*Less frequent*	Gynaecomastia
General disorders 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, such as COLEROS, the incidence of adverse drug reactions tends to be dose dependent.

Renal effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with COLEROS. Shifts in urine protein from none or trace to ++ 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 + 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 COLEROS 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 COLEROS-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 (>5xULN), treatment should be discontinued (see section 4.4).

Liver effects:

As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; 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 >10xULN 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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: HMG-CoA reductase inhibitors, ATC code: C10A A07

Mechanism of action

Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3- hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for cholesterol lowering.

Rosuvastatin produces its lipid-modifying effects in 2 ways; it increases the number of hepatic LDL receptors on the cell-surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of VLDL, thereby reducing the total number of VLDL and LDL particles.

High density lipoprotein (HDL), which contains ApoA-I is involved, amongst other things, in transport of cholesterol from tissues back to liver (reverse cholesterol transport).

Rosuvastatin reduces elevated LDL-cholesterol, total cholesterol and triglycerides and increases HDL-cholesterol. It also lowers ApoB, non-HDL-C, VLDL-C, VLDL-TG and increases ApoA-I (see Table 3 below). Rosuvastatin also lowers the LDL-C/HDLC, total C/HDL-C and non-HDL-C/HDL-C and the ApoB/ApoA-I ratios.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Rosuvastatin is taken up extensively by the liver which is the primary site of cholesterol synthesis and LDL- C clearance. The volume of distribution of rosuvastatin is approximately 134 L. Approximately 90 % of rosuvastatin is bound to plasma proteins, mainly to albumin.

Biotransformation

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

Elimination

Approximately 90 % of the rosuvastatin dose is excreted unchanged in the faeces (consisting of absorbed and non-absorbed active substance) and the remaining part is excreted in urine. Approximately 5 % is excreted unchanged in urine. The plasma elimination half-life is approximately 19 hours. The elimination half-life does not increase at higher doses. The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21.7 %). As with other HMG-CoA reductase inhibitors, the hepatic uptake of rosuvastatin involves the membrane transporter OATP-C. This transporter is important in the hepatic elimination of rosuvastatin.

Linearity

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

Special populations

Age and sex:

There was no clinically relevant effect of age or sex on the pharmacokinetics of rosuvastatin in adults. The exposure in children and adolescents with heterozygous familial hypercholesterolemia appears to be similar to that in adult patients.

Race:

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Koreans) compared with Caucasians; Asian-Indians show an approximate 1.3-fold elevation in median AUC and C_{max}. A population pharmacokinetic analysis revealed no clinically relevant differences in pharmacokinetics between Caucasian and Black groups.

Renal insufficiency:

In a study in subjects with varying degrees of renal impairment, mild to moderate renal disease had no influence on plasma concentration of rosuvastatin or the N-desmethyl metabolite. Subjects with severe impairment (CrCl <30 ml/min) had a 3-fold increase in plasma concentration compared to healthy volunteers.

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 COLEROS 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 that in adult patients. Rosuvastatin exposure was predictable with respect to dose and time over a 2-year period.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenicity potential. Specific tests for effects on hERG have not been evaluated. Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels were as follows: In repeated-dose toxicity studies histopathologic liver changes likely due to the pharmacologic action of rosuvastatin were observed in mouse, rat, and to a lesser extent with effects in the gall bladder in dogs, but not in monkeys. In addition, testicular toxicity was observed in monkeys and dogs at higher dosages. Reproductive toxicity was evident in rats, with reduced litter sizes, litter weight and pup survival observed at maternally toxic doses, where systemic exposures were several times above the therapeutic exposure level.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Sodium hydrogen carbonate
Cellulose, microcrystalline
Crospovidone
Magnesium stearate

Tablet coat: Opadry II pink 32K540023
Hypromellose (15 mPas)
Lactose monohydrate
Titanium dioxide
Triacetin
Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container.

6.5 Nature and contents of container

COLEROS film-coated tablets are packed in:

OPA/Al/PVC-Aluminium blisters strips in an outer carton. 10 Tablets are packed per blister and three blisters are packed in an outer carton. Pack size: 30's.

6.6 Special precautions for disposal and other handling

No Special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8. REGISTRATION NUMBER(S)

COLEROS 5	55/7.5/0022
COLEROS 10	55/7.5/0023
COLEROS 20	55/7.5/0024
COLEROS 40	55/7.5/0025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 September 2022

10. DATE OF REVISION OF THE TEXT

20 July 2023