PROPOSED PROFESSIONAL INFORMATION FOR STORWIN

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

STORWIN® 10 mg film-coated tablets

STORWIN® 20 mg film-coated tablets

STORWIN® 40 mg film-coated tablets

COMPOSITION:

STORWIN 10 mg: Each film-coated tablet contains 10 mg of rosuvastatin as rosuvastatin calcium.

STORWIN 20 mg: Each film-coated tablet contains 20 mg of rosuvastatin as rosuvastatin calcium.

STORWIN 40 mg: Each film-coated tablet contains 40 mg of rosuvastatin as rosuvastatin calcium.

Inactive excipients include: colloidal anhydrous silica, croscarmellose sodium, hypromellose 2910/5, iron oxide red, lactose monohydrate, macrogol 6 000, magnesium stearate, microcrystalline cellulose, talc and titanium dioxide.

Contains sugar:

STORWIN 10 mg: 60 mg lactose monohydrate per film-coated tablet.

STORWIN 20 mg: 120 mg lactose monohydrate per film-coated tablet.

STORWIN 40 mg: 240 mg lactose monohydrate per film-coated tablet.

CATEGORY AND CLASS:

A 7.5 Serum-cholesterol reducers.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mechanism of action:

Rosuvastatin exerts its effect through a mevalonic acid-like moiety that competitively inhibits HMG-CoA reductase. By reducing the conversion of HMG-CoA to mevalonate, rosuvastatin inhibits the early and rate-limiting step in cholesterol biosynthesis.

The primary site of action is the liver, the target organ for cholesterol-lowering effects.

Rosuvastatin increases the number of hepatic low density lipoprotein (LDL) receptors on the cell-surface, enhancing uptake and catabolism of LDL and inhibits the hepatic synthesis of very low density lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.

Pharmacokinetic properties:

Absorption:

Maximum rosuvastatin plasma concentrations are achieved approximately 5 hours after oral administration.

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 is approximately 134 L. Approximately 90 % of rosuvastatin is bound to plasma proteins, mainly to albumin.

Metabolism:

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 principle isoenzyme involved while 2C19, 3A4 and 2D6 were involved to a lesser extent.

The main metabolites identified were the *N*-desmethyl and lactone metabolites. The *N*-desmethyl metabolite was approximately 50 % less active than rosuvastatin whereas the lactone form was considered clinically inactive. Rosuvastatin accounts for greater than 90 % of the circulating HMG-CoA reductase inhibitor activity.

Excretion:

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 and does not increase at higher doses.

The geometric mean plasma clearance is approximately 50 litres/hour (coefficient of variation 21,7 %).

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 linearly in proportion to dose. There are no changes in pharmacokinetic parameters following multiple daily doses.

Special populations:

Race:

Pharmacokinetic studies show an approximate 2-fold elevation in median AUC and C_{max} in Asian subjects (Japanese, Chinese, Filipino, Vietnamese and Korean) 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 among Caucasian, Hispanic and Black or Afro-Caribbean groups (see DOSAGE AND DIRECTIONS FOR USE).

Renal insufficiency:

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

Haemodialysis is unlikely to be of benefit for rosuvastatin removal.

Hepatic insufficiency:

See WARNINGS AND SPECIAL PRECAUTIONS.

INDICATIONS:

STORWIN is indicated for patients with primary hypercholesterolaemia (Type IIa excluding heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (Type IIb) and

hypertriglyceridaemia (Type IV), as an adjunct to diet when response to diet and exercise is inadequate.

STORWIN is indicated in patients with homozygous familial hypercholesterolaemia as an adjunct to diet and other lipid-lowering treatments (e.g. LDL apheresis), or if these treatments are not appropriate.

The 40 mg STORWIN tablet should only be considered in patients with severe hypercholesterolaemia, excluding heterozygous familial hypercholesterolaemia, and high cardiovascular risk, who do not achieve their treatment goal on the 20 mg dose or alternative therapy.

CONTRAINDICATIONS:

STORWIN tablets are contraindicated:

- in patients with hypersensitivity to rosuvastatin or other HMG-CoA reductase inhibitors or to any of the excipients of STORWIN (see COMPOSITION)
- in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminases elevation exceeding 3 x the upper limit of normal (ULN)
- in patients with severe renal impairment (creatinine clearance < 30 ml/min)
- in patients with myopathy
- in concomitant use with ciclosporin (see INTERACTIONS)
- during pregnancy or lactation and in women of childbearing potential who are not using appropriate contraceptive measures (see HUMAN REPRODUCTION).

STORWIN 40 mg is also contraindicated in patients with predisposing 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 INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS:

Before treatment:

STORWIN contains rosuvastatin, an HMG-CoA reductase inhibitor which should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis. Such factors include:

- renal impairment
- hypothyroidism
- personal or family history of hereditary muscular disorders
- previous history of muscular toxicity with another HMG-CoA reductase inhibitor or fibrate
- alcohol abuse
- age > 70 years
- situations where an increase in plasma levels may occur (see PHARMACOLOGICAL ACTION)
- concomitant use of fibrates (see INTERACTIONS).

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

Protease inhibitors:

The concomitant use of STORWIN, in patients with HIV, with various protease inhibitors in combination with ritonavir is not recommended as studies have shown an increase in the AUC and C_{max} of rosuvastatin (see INTERACTIONS).

Hepatic effects:

STORWIN should 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. STORWIN should be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of

normal. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.

In patients with secondary hypercholesterolaemia caused by hypothyroidism or nephritic syndrome, the underlying disease should be treated prior to initiating therapy with STORWIN (see DOSAGE AND DIRECTIONS FOR USE).

Renal effects:

Proteinuria, detected by dipstick testing and mostly tubular in origin has been observed in patients treated with rosuvastatin, in particular STORWIN 40 mg. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from rosuvastatin clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease (see SIDE EFFECTS).

The reporting rate for serious renal events is higher at the 40 mg dose. An assessment of renal function should be considered during follow-up of patients treated with a dose of 40 mg.

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. uncomplicated myalgia, myopathy (including myositis) and rhabdomyolysis, have been reported in patients treated with rosuvastatin and in particular with doses > 20 mg STORWIN. Cases of rhabdomyolysis have been reported with the use of ezetimibe in combination with HMG-CoA reductase inhibitors. A pharmacodynamic interaction cannot be excluded (see INTERACTIONS) and caution should be exercised with the combined use.

The reporting rate for rhabdomyolysis is higher at the 40 mg dose of rosuvastatin.

Creatine kinase measurement:

Creatine kinase (CK) should not be measured following strenuous exercise or in the presence of a plausible alternative cause of CK increase which may confound interpretation of the 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 with STORWIN should not be started.

Whilst on treatment:

Patients who develop any signs or symptoms suggestive of myopathy should have their creatine kinase (CK) levels measured. STORWIN therapy should 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 reintroducing STORWIN 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 very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including STORWIN. 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 HMG-CoA reductase inhibitors together with ciclosporin, fibric acid derivatives, including gemfibrozil, nicotinic acid, azole antifungals and macrolide antibiotics.

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

STORWIN 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 INTERACTIONS). Patients should be advised to seek medical advice immediately if they experience any symptoms of muscle weakness, pain or tenderness. Statin therapy may be reintroduced 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 co-administration of STORWIN and fusidic acid should only be considered on a case by case basis and under close medical supervision.

STORWIN should be prescribed with caution in patients with predisposing factors for myopathy, such as those described at the beginning of this section (see *Before treatment*).

STORWIN should be temporarily withheld in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of renal failure, secondary to rhabdomyolysis (e.g. sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine and electrolyte disorders; or uncontrolled seizures).

Race:

Pharmacokinetic studies show an increase in exposure in Asian subjects compared to Caucasians (see DOSAGE AND DIRECTIONS FOR USE and Pharmacokinetic properties).

Interstitial lung disease:

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

Diabetes mellitus:

Rosuvastatin (as in STORWIN) may raise blood glucose and 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 STORWIN and therefore should not be a reason for stopping STORWIN treatment. Patients at risk (fasting glucose 5,6 to 6,9 mmol/l, body mass index > 30 kg/m^2, raised triglycerides, hypertension) should

be monitored.

Other:

- Liver enzyme tests should be performed in patients before initiating STORWIN therapy and as clinically indicated thereafter. If serious liver injury with clinical symptoms and/or hyperbilirubinaemia or jaundice occurs during treatment, therapy should be interrupted. If an alternate etiology is not found, STORWIN should not be restarted.
- Increases in glycosylated haemoglobin (HbA1c), fasting serum glucose levels and worsening of glycaemic control have been reported with the use of statins, such as STORWIN. STORWIN should therefore be used with care in patients with Type 2 diabetes.
- There have been reports of cognitive impairment (such as memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with statin use such as STORWIN. These reported symptoms were generally not serious and reversible upon discontinuation with variable times to symptom onset (between a day to years) and symptom resolution with a median of 3 weeks.
- Memory loss/impairment and confusion have been reported with rosuvastatin such as STORWIN in patients over the age of 50. These events were generally not serious and were reversible upon discontinuation of rosuvastatin.

Lactose intolerance:

STORWIN tablets contain lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take STORWIN.

Effects on ability to drive and use machines:

From the safety profile, STORWIN is not expected to adversely affect the ability to drive or use machines. However, it should be taken into account that dizziness may occur during treatment (see SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS). Therefore, patients

taking STORWIN should not drive or operate machinery until their individual susceptibility to dizziness is known.

INTERACTIONS:

Interaction with other medicines and other forms of interactions:

Transporter protein inhibitors:

Rosuvastatin is a substrate for certain transporter proteins including the hepatic uptake transporter OATP1B1 and efflux transporter BCRP. Concomitant administration of STORWIN with medicines that are inhibitors of these transporter proteins may result in increased rosuvastatin plasma concentrations and an increased risk of myopathy (see WARNINGS AND SPECIAL PRECAUTIONS).

Ciclosporin: (see CONTRAINDICATIONS)

During concomitant treatment with ciclosporin, STORWIN AUC values may on average be 7 times higher than those in patients not taking ciclosporin. This effect was shown in healthy volunteers. STORWIN is contraindicated in patients receiving concomitant ciclosporin. Concomitant administration of the two medicines does not affect plasma concentrations of ciclosporin.

Vitamin K antagonists such as warfarin:

Concomitant treatment with vitamin K antagonists (e.g. warfarin) may result in an increase in international normalised ratio (INR). Discontinuation or down-titration of STORWIN may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.

Gemfibrozil and other lipid-lowering products:

Concomitant use of STORWIN and gemfibrozil may result in a 2-fold increase in rosuvastatin C_{max} and AUC (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

Based on data from specific interaction studies, no relevant pharmacokinetic interaction with fenofibrate is expected. However, a pharmacodynamic interaction may occur. Gemfibrozil,

fenofibrate, other fibrates and lipid-lowering doses ≥ to 1 g/day) of niacin (nicotinic acid) increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone. The 40 mg dose is contraindicated with concomitant use of a fibrate (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS). These patients should start with a 5 mg dose (halve a 10 mg tablet with a break-line).

Ezetimibe:

Concomitant use of STORWIN and ezetimibe will not result in any change to AUC or C_{max} for either medicine. However cases of rhabdomyolysis have been reported in combination with rosuvastatin (see WARNINGS AND SPECIAL PRECAUTIONS).

Protease inhibitors: (see WARNINGS AND SPECIAL PRECAUTIONS)

Increased systemic exposure to rosuvastatin has been observed in subjects in pharmacokinetic studies receiving rosuvastatin with various protease inhibitors in combination with ritonavir. The increase in systemic exposure to rosuvastatin may lead to increased incidence of adverse effects.

Antacids:

The simultaneous dosing of STORWIN with an antacid suspension containing aluminium and magnesium hydroxide can result in a decrease in rosuvastatin plasma concentration of approximately 50 %. This effect is mitigated when the antacid is dosed 2 hours after STORWIN. The clinical relevance of this interaction has not been studied.

Erythromycin:

Concomitant use of STORWIN and erythromycin can result in a 20 % decrease in $AUC_{(0-t)}$ and a 30 % decrease in C_{max} of rosuvastatin. This interaction may be caused by the increase in gastrointestinal motility caused by erythromycin.

Oral contraceptive/hormone replacement therapy (HRT):

Concomitant use of STORWIN and an oral contraceptive can result 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. Although there are no pharmacokinetic data available in women taking concomitant HRT, 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:

The risk of myopathy including rhabdomyolysis may be increased by the concomitant administration of systemic fusidic acid with STORWIN. 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, STORWIN treatment should be discontinued throughout the duration of the fusidic acid treatment (see WARNINGS AND SPECIAL PRECAUTIONS).

Cytochrome P450 enzymes:

Rosuvastatin is neither an inhibitor nor an inducer of cytochrome P450 isoenzymes. In addition, the active substance is a poor substrate for these isoenzymes. No clinically relevant interactions have been observed during concomitant use with fluconazole (an inhibitor of CYP2C9 and CYP3A4) or ketoconazole (an inhibitor of CYP2A6 and CYP3A4). Concomitant administration with itraconazole (an inhibitor of CYP3A4) can result in a 28 % increase in AUC of STORWIN. This increase is not considered clinically significant. Therefore, interactions resulting from cytochrome P450-mediated metabolism are not expected.

Interactions requiring STORWIN dose adjustments (see also Table 1): When it is necessary to co-administer STORWIN with other medicines known to increase exposure to rosuvastatin, doses of STORWIN should be adjusted. Start with a 5 mg once daily dose of STORWIN if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of STORWIN should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicines, for example a 20 mg dose of STORWIN with gemfibrozil (1,9-fold increase), and a 10 mg dose of STORWIN with combination atazanavir/ritonavir (3,1-fold increase).

Table 1: Effect of co-administered medicines on STORWIN exposure (AUC; in order of decreasing magnitude)

Interacting medicine dose regimen	**STORWIN dose regimen**	**Change in rosuvastatin AUC***
Ciclosporin 75 mg BID to 200 mg BID, 6 months	10 mg OD, 10 days	7,1-fold ↑
Atazanavir 300 mg/ritonavir 100 mg OD, 8 days	10 mg, single dose	3,1-fold ↑
Simeprevir 150 mg OD, 7 days	10 mg, single dose	2,8-fold ↑
Lopinavir 400 mg/ritonavir 100 mg BID, 17 days	20 mg OD, 7 days	2,1-fold ↑
Clopidogrel 300 mg loading dose, 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 ↑
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	20% ↓
Baicalin 50 mg TID, 14 days	20 mg, single dose	47% ↓
*Data given as ×-fold change represent a simple ratio between co-administration and STORWIN alone. Data given as % change represent % difference relative to STORWIN alone. Increase is indicated as "↑", no change as "↔", decrease as "↓". **Several interaction studies have been performed at different STORWIN dosages, the table shows the most significant ratio. OD = once daily; BID = twice daily; TID = three times daily; QID = four times daily.		

HUMAN REPRODUCTION:

Pregnancy:

STORWIN is contraindicated in pregnancy (see CONTRAINDICATIONS).

STORWIN may cause serious congenital defects if it is taken during pregnancy.

If a patient becomes pregnant during use of STORWIN, treatment should be discontinued immediately.

Women of childbearing potential:

Women of childbearing potential should use appropriate contraceptives during treatment.

Lactation:

STORWIN is contraindicated in lactation (see CONTRAINDICATIONS).

The active substance in STORWIN is excreted in the milk of rats. There are no data with respect to excretion in milk in humans. A patient taking STORWIN should not breastfeed their infant.

DOSAGE AND DIRECTIONS FOR USE:

Before treatment initiation, the patient should be placed on a standard cholesterol-lowering diet that should continue during treatment. The dosage range for STORWIN is 5 – 40 mg orally once a day. The recommended starting dose is 5 mg orally once daily in both statin-naïve and patients switched from another HMG-CoA reductase inhibitor. Administration of a 5 mg dose can be achieved by halving a 10 mg tablet which has a break-line.

The choice of starting dose should take into account the individual patient's cholesterol level, cardiovascular risk and the potential risk for adverse reactions (see WARNINGS AND SPECIAL

PRECAUTIONS). A dosage adjustment to the next level can be made after 4 weeks if necessary (see PHARMACOLOGICAL ACTION).

In light of the increased reporting rate of adverse reactions with the 40 mg dose compared to the lower doses (see WARNINGS AND SPECIAL PRECAUTIONS), a final titration to the maximum dose of 40 mg should only be considered after another 4-week period and only in patients with severe hypercholesterolaemia at high cardiovascular risk (in particular those with familial hypercholesterolaemia) who do not achieve their treatment goal on 20 mg, and in whom routine follow-up will be performed. Specialist supervision is recommended when the 40 mg dose is initiated.

The dosage of STORWIN should be individualised according to the goal of therapy and patient response. The majority of patients are controlled at the 10 mg dose.
STORWIN may be given at any time of the day, with or without food.

Primary hypercholesterolaemia, mixed dyslipidaemia and isolated hypertriglyceridaemia:
The recommended starting dose is 5 mg once a day (halve a 10 mg tablet with a break-line).
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 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.

Paediatric use:
STORWIN is not recommended for children due to insufficient data concerning its safety and efficacy.

Use in the elderly:

A starting dose of 5 mg (halve a 10 mg tablet with a break-line) is recommended in patients over 70 years old. No other dose adjustment is necessary in relation to age.

Dosage in patients with renal impairment:

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

The recommended starting dose is 5 mg (halve a 10 mg tablet with a break-line) in patients with moderate renal impairment (creatinine clearance of 30 – 60 ml/min).

The 40 mg dose is contraindicated in patients with moderate renal impairment (see CONTRAINDICATIONS).

The use in patients with severe renal impairment is contraindicated for all doses (see CONTRAINDICATIONS).

Dosage in patients with hepatic impairment:

The usual starting dose applies in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment should start therapy with STORWIN 5 mg. Increased systemic exposure to rosuvastatin has been observed in these patients therefore the use of doses above 10 mg should be carefully considered.

There was no increase in systemic exposure in subjects with Child-Pugh scores of 7 or below. However, increased systemic exposure has been observed in subjects with Child-Pugh scores of 8 and 9. In these patients, an assessment of renal function should be performed. There is no experience in subjects with Child-Pugh scores above 9.

STORWIN is contraindicated in patients with active liver disease (see CONTRAINDICATIONS).

Race:

Increased systemic exposure has been seen in Asian subjects (see Pharmacokinetic properties: Special populations). The recommended starting dose is 5 mg (halve a 10 mg tablet with a break-line) for patients of Asian ancestry.

The 40 mg dose is contraindicated in these patients (see CONTRAINDICATIONS and WARNINGS

AND SPECIAL PRECAUTIONS).

Dosage in patients with predisposing factors to myopathy:

The recommended starting dose is 5 mg (halve a 10 mg tablet with a break-line) in patients with predisposing factors to myopathy (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Concomitant therapy:

STORWIN may have an additive effect in lowering triglycerides when used in combination with fenofibrate and may increase HDL-C levels when used in combination with niacin.

STORWIN can also be used in combination with bile acid sequestrants (see WARNINGS AND SPECIAL PRECAUTIONS).

Interactions requiring dose adjustments:

Gemfibrozil:

Patients taking a combination of STORWIN and gemfibrozil should start therapy with STORWIN 5 mg (halve a 10 mg tablet with a break-line) once daily and should not exceed a dose of STORWIN 20 mg once daily (see INTERACTIONS).

SIDE EFFECTS:

Where no frequency data are available, the term ‘frequency unknown’ has been used. The incidence of adverse drug reactions tends to increase with increasing dose.

Blood and lymphatic system disorders:

Less frequent: anaemia, thrombocytopenia

Immune system disorders:

Less frequent: hypersensitivity reactions including angioedema

Infections and infestations:

Less frequent: infection

Endocrine disorders:

Frequent: diabetes mellitus[1]

Psychiatric disorders:

Less frequent: anxiety, depression, insomnia

Nervous system disorders:

Frequent: headache, dizziness, vertigo, vomiting

Less frequent: polyneuropathy, paraesthesia, cognitive impairment such as memory loss, forgetfulness, amnesia, memory impairment and confusion

Frequency unknown: peripheral neuropathy, sleep disturbances (including insomnia and nightmares)

Cardiac disorders:

Less frequent: angina pectoris

Vascular disorders:

Less frequent: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders:

Frequent: pharyngitis

Less frequent: asthma, bronchitis, dyspnoea, dyspepsia, rhinitis, sinusitis

Frequency unknown: cough

Gastrointestinal disorders:

Frequent: constipation, nausea, abdominal pain

Less frequent: pancreatitis, gastritis

Frequency unknown: diarrhoea

Metabolism and nutrition disorders:

Frequent: increased serum glucose levels

Hepatobiliary disorders:

Less frequent: jaundice, hepatitis, increased hepatic transaminases

Skin and subcutaneous tissue disorders:

Less frequent: pruritus, rash, urticaria, ecchymosis

Frequency unknown: Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders:

Frequent: myalgia

Less frequent: myopathy (including myositis), rhabdomyolysis, arthralgia, arthritis, back pain, hypertonia

Frequency unknown: immune-mediated necrotising myopathy, tendon disorders (sometimes complicated by rupture)

Renal and urinary disorders:

Less frequent: haematuria, proteinuria

Reproductive system and breast disorders

Less frequent: gynaecomastia

General disorders and administration site conditions:

Frequent: asthenia

Frequency unknown: oedema

Investigations:

A dose-related increase in liver transaminases and creatine kinase (CK) has been observed in patients. Abnormal urinalysis testing (dipstick-positive proteinuria with haematuria) has been seen. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on continued therapy, and is not predictive of acute or progressive renal disease.

[1]Frequency will depend on the presence or absence of risk factors (fasting blood glucose ≥ 5,6 mmol/l, BMI > 30 kg/m^2, raised triglycerides, history of hypertension).
The incidence of side effects tends to be dose dependent.

Renal effects: Proteinuria, detected by dipstick testing and mostly tubular in origin, has been observed in patients treated with rosuvastatin. Shifts in urine protein from none or trace to ++ or more were seen in < 1 % of patients at some time during treatment with 10 mg and 20 mg, and in approximately 3 % of patients treated with 40 mg. A minor increase in shift from none or trace to + was observed with the 20 mg dose. In most cases, proteinuria decreases or disappears spontaneously on continued therapy. Review of data from clinical trials and post-marketing experience to date has not identified a causal association between proteinuria and acute or progressive renal disease.

Haematuria has been observed in patients treated with rosuvastatin and clinical trial data show that the occurrence is low.

Skeletal muscle effects: Effects on skeletal muscle e.g. myalgia, myopathy (including myositis) and, rarely, rhabdomyolysis with and without acute renal failure have been reported in rosuvastatin-treated patients with all doses and 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 with STORWIN should be discontinued (see WARNINGS AND SPECIAL PRECAUTIONS).

Liver effects: 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 side effects have been reported with some statins:

- sexual dysfunction
- exceptional cases of interstitial lung disease, especially with long term therapy (see WARNINGS AND SPECIAL PRECAUTIONS).

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no specific treatment 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.

IDENTIFICATION:

STORWIN 10 mg: light pink, film-coated, oval, biconvex tablet with halving score.

STORWIN 20 mg: pink, film-coated, oval, biconvex tablet.

STORWIN 40 mg: dark pink, film-coated, oval, biconvex tablet.

PRESENTATION:

The packs consist of 30 tablets each, packed in blister strips, 10 film-coated tablets in each blister, enclosed in a cardboard carton, inclusive of a professional information leaflet.

The blister strips are composed of triple laminated forming material and aluminium lidding material

and are silver in colour.

STORAGE INSTRUCTIONS:

Store at or below 25 °C in the original package. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

Do not remove from outer carton until required for use.

REGISTRATION NUMBERS:

STORWIN 10 mg: 45/7.5/0502

STORWIN 20 mg: 45/7.5/0503

STORWIN 40 mg: 45/7.5/0504

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zentiva South Africa (Pty) Ltd

2 Bond Street

Midrand 1685

South Africa

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 15 August 2013

Date of revision: 25 October 2018

NAMIBIA

SCHEDULING STATUS: NS2

Registration numbers:

STORWIN 10 mg: 15/7.1/0155

STORWIN 20 mg: 15/7.1/0156

STORWIN 40 mg: 15/7.1/0157