

Rosuvastatin Stada 5 mg film-coated tablets
Rosuvastatin Stada 10 mg film-coated tablets
Rosuvastatin Stada 20 mg film-coated tablets
Rosuvastatin Stada 40 mg film-coated tablets

25.8.2014, V1.1

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

PRODUCT NAME 5mg film-coated tablets
PRODUCT NAME 10mg film-coated tablets
PRODUCT NAME 20mg film-coated tablets
PRODUCT NAME 40mg film-coated tablets.

VI.2.1 Overview of disease epidemiology

Hypercholesterolemia

Hypercholesterolemia is a condition characterized by high levels of cholesterol, a specific lipid (fat) in the blood. There are two main types of cholesterol: HDL (high-density lipoprotein) and LDL (low-density lipoprotein). High LDL-cholesterol levels in particular are associated with an increased risk of atherosclerosis and coronary heart disease. Chronically elevated cholesterol levels in the serum over a period of decades can further the formation of plaques in the arteries, which in turn can lead to worsening narrowing (stenosis) or even complete blockage (occlusion) of those arteries. Higher HDL cholesterol levels, on the other hand, are protective. In 2010, just over 13% of population in the US had high total cholesterol levels. Recommendations aimed at reducing the total blood cholesterol and LDL cholesterol levels in adults include a reduction in the intake of saturated fat through diet. In people with very high cholesterol levels, LDL cholesterol levels can often not be controlled by diet alone; in these patients, lipid-lowering medications, and sometimes LDL apheresis (blood filtering) or surgery are required.

Prevention of cardiovascular events

Cardiovascular disease (CVD), an illness involving the heart and/or the blood vessels, is considered to be the leading cause of death worldwide. According to the European Society of Cardiology, CVD causes over 4 million deaths in Europe every year, and 1.9 million deaths in the European Union (EU). CVD has been associated with advanced age, male gender, obesity, high blood pressure, hyperlipidemia and diabetes mellitus amongst other factors; however, the main causes are considered to be lifestyle factors (such as smoking, lack of physical activity, bad diet) that lead to clogging of arteries (atherosclerosis). Therefore, measures for prevention of CVD are currently targeting mainly lifestyle and diet. In patients with a history of CVD, statins (a type of lipid-lowering medication) are found to be effective in preventing further CVD. Statins also appear to be beneficial (decrease in mortality and further heart disease) in patients without a prior history, but with risk factors for CVD.

VI.2.2 Summary of treatment benefits

Rosuvastatin is the active ingredient of PRODUCT NAME.

PRODUCT NAME belongs to the group called 'statins'. It reduces total blood cholesterol by blocking the action of 3-hydroxy-3-methyl-glutaryl-co-enzyme-A (HMG-CoA) reductase, an enzyme in the liver involved in the production of cholesterol.

PRODUCT NAME is used for the treatment of signs of illness (symptoms) associated with:

- Treatment of high high cholesterol level (hypercholesterolemia)
- Prevention of heart attack, stroke or related health problems (Cardiovascular events)

The use in the treatment of high cholesterol was investigated in one large study, with 435 patients with heterozygous familial hypercholesterolemia. Patients were treated with rosuvastatin from 20 mg to 80 mg. Reduction in the level of cholesterol was measured after 12 weeks following step-wise dose increase to a daily dose of 40 mg. The level of cholesterol (LDL-cholesterol) was reduced by 53 %. In another study with 42 patients treated with similar doses, the mean reduction of LDL-cholesterol reduction was 22 %.

The use for prevention of cardiovascular events was investigated in a study involving 984 patients at low risk for coronary heart disease, but with subclinical atherosclerosis (measurement of 'Carotid Intima Media Thickness' as sign of atherosclerosis). For 2 years, patients were treated with either 40 mg rosuvastatin once daily or with placebo. Rosuvastatin significantly slowed the progression of the 'Carotid Intima Media Thickness' compared to placebo. A further study assessed the effect of rosuvastatin on the occurrence of major atherosclerotic cardiovascular events in 17,802 men. Patients were treated with either 20 mg rosuvastatin once daily or with placebo for 2 years. LDL-cholesterol concentration was reduced by 45 % in the rosuvastatin group compared with the placebo group. Further analyses of high-risk subgroups showed beneficial effects on the end-points cardiovascular death, stroke and myocardial infarction, whereas total mortality was unchanged in these high risk groups.

VI.2.3 Unknowns relating to treatment benefits

Experience in children younger than 10 years is limited to a small number of children (aged between 8 and 10 years) with familial hypercholesterolemia.

There is no experience in subjects with severe hepatic impairment (Child-Pugh scores above 9).

Animal studies provided limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.

Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion into breastmilk in humans.

Studies to determine the effect of rosuvastatin on the ability to drive and use machines have not been conducted.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Muscle damage (Rhabdomyolysis)	Muscle damage may affect up to 1 in 1,000 people treated with PRODUCT NAME. A risk of muscle damage has	Patients at risk of muscular disease should NOT be treated with the highest possible dose (40 mg) of rosuvastatin.

	<p>to be considered in patients to whom any of the following apply:</p> <ul style="list-style-type: none"> • impaired kidney function • reduced function of the thyroid gland • personal or family history of muscular diseases • alcohol abuse • concomitant use of other medicines as described in the Package Leaflet • increased level of creatinine kinase (CK) in blood before start of the treatment • age 70 years or older <p>Muscle symptoms are more common in children and adolescents than in adults.</p>	<p>If CK levels are significantly elevated at baseline (5 time the upper limit of normal) treatment should not be started.</p> <p>Stop taking the drug and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than you might expect. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely these have gone on to become a potentially life threatening muscle damage known as rhabdomyolysis.</p>
<p>Muscle ache and pain, increased muscle parameters in blood (creatinine kinase and myoglobin) and in urine (myoglobin) in association with muscle damage</p> <p>(Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinemia (in the setting of rhabdomyolysis and myopathy))</p>	<p>Muscle pain may affect up to 1 in 10 people treated with PRODUCT NAME..</p> <p>The frequency of muscle weakness is unknown.</p> <p>A risk of muscle damage has to be considered in patients to whom any of the following apply:</p> <ul style="list-style-type: none"> • impaired kidney function • reduced function of thyroid gland • personal or family history of muscular diseases • age of 70 years and older • alcohol abuse • concomitant use of other medicines as described in the Package Leaflet • increased level of creatinine kinase (CK) in blood before start of the treatment. <p>Muscle symptoms are more common in children and adolescents than in adults.</p>	<p>Treatment with the highest possible dose (40 mg) of rosuvastatin is not allowed in patients at risk of muscle disease.</p> <p>If CK levels are significantly elevated at baseline (5 time the upper limit of normal), treatment should not be started.</p> <p>Therapy should be discontinued if CK levels are markedly elevated (more than 5 time the upper limit of normal) or if muscular symptoms are severe and cause daily discomfort (even if CK levels are not above this level).</p> <p>Stop taking the drug and talk to your doctor immediately if you have any unusual aches or pains in your muscles which go on for longer than you might expect. As with other statins, a very small number of people have experienced unpleasant muscle effects and rarely</p>

		these have gone on to become a potentially life threatening muscle damage known as rhabdomyolysis.
<p>Increased levels of liver enzymes, inflammation of the liver, yellowing of the skin and eyes</p> <p>(Increased transaminases, hepatitis, jaundice)</p>	<p>Increased levels of liver enzymes may affect up to 1 in 1,000 people treated with PRODUCT NAME. The majority of cases were mild, asymptomatic and transient.</p> <p>Inflamed liver and yellowing of the skin and eyes may affect up to 1 in 10,000 people treated with PRODUCT NAME..</p>	<p>Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease.</p> <p>Liver function test are usually carried out before and during treatment with the drug. Rosovastatin should not be started, be discontinued or the dose reduced if the level of serum transaminases is greater than 3 times the upper limit of normal.</p> <p>If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.</p>
<p>Inflammation of the pancreas</p> <p>(Pancreatitis)</p>	<p>Inflammation of the pancreas may affect up to 1 in 1,000 people treated with PRODUCT NAME.</p>	<p>Severe stomach pain can be a sign for an inflamed pancreas. Talk to your doctor or pharmacist if you think you might have pancreatitis. They will advise you on the best course of action.</p> <p>Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.</p>
<p>Memory Loss</p> <p>(Memory Loss)</p>	<p>Memory loss may affect up to 1 in 10,000 people treated with PRODUCT NAME.</p>	<p>Talk to your doctor or pharmacist if you notice yourself becoming more forgetful during treatment with rosuvastatin.</p>

<p>Increase in the amount of protein in the urine</p> <p>(Proteinuria)</p>	<p>Increase in the amount of protein in the urine may affect up to 1 in 10 people receiving PRODUCT NAME 40mg, and up to 1 in a 100 people receiving PRODUCT NAME 5mg, 10mg or 20mg.</p> <p>This usually returns to normal on its own without having to stop taking your rosuvastatin.</p>	<p>An increased protein level in your urine can be discovered during a urine test. Your doctor will advise you on the best course of action.</p> <p>If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.</p>
<p>Serious blistering condition of the skin, mouth, eyes and genitals</p> <p>(Stevens-Johnson syndrome and Toxic epidermal necrolysis)</p>	<p>Serious blistering conditions of the skin, mouth, eyes and genitals have occurred in patients treated with PRODUCT NAME. The frequency of these events is unknown.</p>	<p>If you notice blistering of your skin, mouth or genitals, immediately stop taking PRODUCT NAME and consult a doctor.</p> <p>If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.</p>
<p>Diabetes</p> <p>(Diabetes mellitus)</p>	<p>Diabetes may affect up to 1 in 10 people treated with PRODUCT NAME.</p> <p>Patients with high levels of sugars and fats in their blood, who are overweight or have high blood pressure are at risk of developing diabetes.</p>	<p>Your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes.</p> <p>If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of</p>

		developing adverse drug reactions.
Depression (Depression)	Depression has been observed in patients treated with PRODUCT NAME; the frequency of this event is unknown.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Sleep disturbances, including insomnia and nightmares (Sleep disorders including insomnia and nightmares)	Sleep disturbances, including an inability to sleep and nightmares, have been observed in patients treated with PRODUCT NAME. The frequency of this event is unknown.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Muscle damage caused by immune disorders (Immune-mediated necrotizing myopathy)	Immune-mediated necrotising myopathy (a muscle disorder characterised by cell death and caused by the body's own immune system) has been observed in patients treated with PRODUCT NAME. The frequency of this event cannot be estimated.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Decreased platelet count (Thrombocytopenia/decreased platelet count)	Decreased platelet count may affect up to 1 in 1.000 people treated with PRODUCT NAME.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.

<p>Tendon injuries (Tendon disorders)</p>	<p>The frequency of tendon injuries is unknown.</p>	<p>If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.</p>
<p>Interactions with ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe (Drug-drug interactions including, ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe)</p>	<p>A warning concerning the treatment with following drugs is stated in the Package leaflet:</p> <ul style="list-style-type: none"> • ciclosporin (used for example, after organ transplants), • ritonavir with lopinavir and/or atazanavir (used to treat the HIV infection, • fibrates (such as gemfibrozil, fenofibrate), • any other medicine used to lower cholesterol (such as ezetimibe). 	<p>Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.</p> <p>Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimize the risk of developing adverse drug reactions.</p>

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
<p>Renal failure (including acute and chronic renal failure) and renal impairment</p>	<p>Patients treated with the medicinal product may be at an increased risk of developing this safety concern.</p> <p>Renal impairment is considered as predisposing factor for myopathy/rhabdomyolysis.</p> <p>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, where it was transient or intermittent in most cases. Proteinuria has not been shown to be predictive of acute or progressive renal disease.</p> <p>Cases haematuria have been reported from post-marketing experience in temporal association with the intake of rosuvastatin. However, a causal relationship has not been established.</p> <p>The reporting rates for serious renal events are higher at the</p>

	40 mg dose.
Hepatic failure: including hepatic necrosis and fulminant hepatitis	<p>Patients treated with the medicinal product may be at an increased risk of developing this safety concern.</p> <p>Cases increased hepatic transaminases, jaundice and hepatitis have been reported from post-marketing experience in temporal association with the intake of rosuvastatin. However, a causal relationship has not been established.</p> <p>The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is higher at the 40 mg dose.</p>
Peripheral neuropathy	<p>Patients treated with the medicinal product may be at an increased risk of developing this safety concern.</p> <p>Cases increased peripheral neuropathy have been reported very rarely from post-marketing experience in temporal association with the intake of rosuvastatin. Polyneuropathy was reported rarely. However, a causal relationship has not been established.</p>
Amyotrophic lateral sclerosis	Patients treated with the medicinal product may be at an increased risk of developing this safety concern.
Interstitial lung disease	<p>Patients treated with the medicinal product may be at an increased risk of developing this safety concern.</p> <p>Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Symptoms can 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 should be discontinued.</p>
Drug-drug interaction with fibrates (other than gemfibrozil)	<p>Concomitant use of fibrates is considered as risk factor for development of myopathy/rhabdomyolysis.</p> <p>Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamic interaction may occur. Fibrates 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 of rosuvastatin is contraindicated with concomitant use of a fibrate.</p>

Missing information

Risk	What is known
Severe hepatic impairment	There is no experience in subjects with severe hepatic impairment (Child-Pugh scores above 9). Rosuvastatin is

	<p>contraindicated in patients with active liver disease. 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 considered.</p>
Elderly subjects	<p>A start dose of 5 mg is recommended in patients aged 70 years and older. No other dosage adjustments are necessary in relation to age</p>
Paediatric subjects	<p>After 52 weeks of study treatment, no effect on growth, weight, BMI or sexual maturation was detected. The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (more than 1 year) on puberty are unknown.</p> <p>Creatine kinase elevations (above 10 time the upper limit of normal) 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. In other respects, the safety profile of rosuvastatin was similar in children and adolescents compared to adults.</p>
Severe renal impairment	<p>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 and a 9-fold increase in the N-desmethyl metabolite concentration compared to healthy volunteers.</p> <p>Therefore the recommended start dose is 5 mg in patients with moderate renal impairment (creatinine clearance < 60 ml/min). The 40 mg dose is contraindicated in patients with moderate renal impairment. The use of rosuvastatin in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated for all doses.</p>
Pregnant or lactating women	<p>Since cholesterol and other products of cholesterol biosynthesis are essential for the development of the foetus, the potential risk from inhibition of HMG-CoA reductase outweighs the advantage of treatment during pregnancy. Animal studies provide limited evidence of reproductive toxicity. If a patient becomes pregnant during use of this product, treatment should be discontinued immediately.</p> <p>Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.</p>
Asian population: increased plasma exposure	<p>Pharmacokinetic studies show an increase in exposure in Asian subjects compared with Caucasians. The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.</p>
Very low LDL-C levels	<p>Very low LDL-C levels can occur. Although it is the aim of lipid-lowering therapy to keep LDL-C levels low (below 100</p>

	mg/dL), the effect of very low LDL-C levels is unknown.
Genetic polymorphisms: increased plasma exposure	Specific types of genetic polymorphisms are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of polymorphisms, a lower daily dose of rosuvastatin is recommended.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable.