

VI.2 Elements for a Public Summary

VI.2.1 *Overview of disease epidemiology*

People with high blood cholesterol levels have a greater risk of having a heart attack, stroke or other related cardiovascular disease. This is because cholesterol and other fatty substances (lipids) may build up on the inside wall of blood vessels causing them to narrow. Sometimes blood clots form which block the blood vessels completely. Cardiovascular diseases such as strokes and heart attacks cause almost 1 in 3 deaths worldwide each year.

High cholesterol levels are common throughout the world, but are more common in high-income than low-income regions. In high-income regions such as Europe, the United States, Canada and Japan, more than half of adults have high cholesterol levels.

Sometimes cholesterol levels can be lowered with changes in diet and increased exercise. However, cholesterol levels are often affected by things that cannot be changed, such as age, sex, or family medical history. Cholesterol levels usually rise steadily with age, but stabilise after middle age. Approximately 1 in 500 people have an inherited disease called familial hypercholesterolaemia, which causes very high cholesterol levels even during childhood.

VI.2.2 *Summary of treatment benefits*

Rosuvastatin is a member of a group of medicines known as ‘statins’. In adults and children ≥ 6 years of age, rosuvastatin is used to lower high levels of cholesterol and other lipids in the blood. By lowering blood lipid levels, rosuvastatin can slow the build up of fatty deposits in the walls of the blood vessels. Therefore the risk of heart attacks, stroke and deaths is lessened.

Rosuvastatin is a medicine for improving blood fat levels and is used together with a low fat diet and exercise with the aim of reducing patients’ levels of triglycerides (a type of fat) and increasing their levels of ‘good’ cholesterol (HDL cholesterol). Rosuvastatin is to be used in adults at high risk of heart disease whose levels of ‘bad’ cholesterol (LDL cholesterol) are high. Rosuvastatin is effective in adults with high blood fat levels, with and without hypertriglyceridaemia (increased type of fat), regardless of race, sex, or age and in special populations such as diabetics, or patients with inherited blood fat increase.

VI.2.3 *Unknowns relating to treatment benefits*

From the data, rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (blood fat increase). In about 80 % of patients treated with 10

mg per day reached the levels of “bad” cholesterol (LDL-C) were reduced to the desirable values. The long-term effects of rosuvastatin (>1 year) on patients below 18 years of age are unknown. The safety and efficacy of use in children younger than 6 years of age has not been studied.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
<p>Muscle effects including potentially life threatening muscle damage (rhabdomyolysis) and other muscle problems such as muscular weakness (myopathy), muscle inflammation (myositis), muscle pain (myalgia), increased creatine kinase in the urine (an enzyme released by damaged muscles) and the presence of myoglobin (carries oxygen in the muscles) in the urine (myoglobinuria).</p>	<p>As with other statins, some people experience unpleasant muscle side effects during rosuvastatin treatment. Muscle pain is common (between 1 in 100 and 1 in 10 patients) and muscle weakness, muscle inflammation or rhabdomyolysis are rare (between 1 in 10,000 and 1 in 1,000 patients). Rhabdomyolysis develops when the muscle fibers are damaged and the myoglobin inside the muscle fibers leaks into the blood. Myoglobin can harm the kidneys and can cause severe kidney damage. Symptoms of rhabdomyolysis include unusually dark coloured urine, decreased urine, and muscle ache, weakness or stiffness. Rhabdomyolysis can be treated, but if it is unrecognised or aggressive, it is a potentially life-threatening condition.</p>	<p>The PIL instructs patients to inform their doctor or pharmacist if they have had repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines. Patients should not to take rosuvastatin if they have repeated or unexplained muscle aches or pains. Prescribing information informs doctors that rosuvastatin should be prescribed with caution in patients who have a higher risk of developing muscle problems and patients developing any signs or symptoms suggestive of muscle problems should have blood tests to determine whether treatment needs to be stopped. The recommended start dose in patients with predisposing factors to myopathy is 5 mg daily.</p>
<p>Increased levels of liver enzymes in the blood (increased transaminases),</p>	<p>Increased transaminases are rare (between 1 in 10000 and 1 in 1000 patients) and jaundice</p>	<p>The PIL instructs patients not to take rosuvastatin if they currently have a disease of</p>

Risk	What is known	Preventability
liver inflammation (hepatitis), yellowing of skin and eyes (jaundice)	and hepatitis are very rare (<1 in 10,000 patients) with rosuvastatin treatment. Elevated liver enzymes in the blood and/or yellow skin and eyes may indicate liver damage. Hepatitis is a term used to describe inflammation (swelling) of the liver. It can occur as a result of a viral infection or because the liver is exposed to harmful substances such as alcohol or drugs. The initial symptoms of hepatitis may be similar to those of the flu, and may include muscle and joint pain, a high temperature (fever) of 38°C or above, feeling or being sick, headache, and occasionally yellowing of the eyes and skin (jaundice). If the hepatitis lasts for a long time, symptoms may include feeling unusually tired all the time, depression, jaundice or a general sense of feeling unwell.	their liver. Before taking their tablets, patients should tell their doctor or pharmacist if they have any problems with their liver or regularly drink large amounts of alcohol. The PIL also informs patients that the doctor may perform a simple blood test (liver function test) before and during rosuvastatin treatment which looks for increased levels of liver enzymes in the blood. Prescribing information informs doctors that rosuvastatin should not be used in patients with active liver disease or with elevated liver enzymes. Liver function tests are recommended before and during treatment.
Inflammation of the pancreas (pancreatitis)	Inflammation of the pancreas is rare (between 1 in 10000 and 1 in 1000 patients) with rosuvastatin treatment. The inflammation is usually caused by gall stones or alcohol, but may also be caused by drugs.	The PIL informs patients that on rare occasions, some people may develop a severe stomach pain (inflamed pancreas). Prescribing information informs doctors that pancreatitis occurs rarely in patients taking rosuvastatin.
Difficulty remembering things (memory loss)	Memory loss is very rare (less than 1 in 10,000 patients) with rosuvastatin treatment.	The PIL informs patients that very rarely a few people may suffer from memory loss while on rosuvastatin treatment. Prescribing information

Risk	What is known	Preventability
		informs doctors that memory loss occurs very rarely in patients taking rosuvastatin.
An increase in the amount of protein in the urine (proteinuria)	Increased protein in the urine is uncommon (between 1 in 100 and 1 in 1000 patients) with rosuvastatin treatment. Although proteinuria can be a sign of kidney damage, in most cases it returns to normal on its own.	The PIL informs patients that an increase in the amount of protein in the urine has been observed with rosuvastatin. This usually returns to normal on its own without having to stop taking rosuvastatin. Prescribing information informs doctors that proteinuria has been seen patients taking higher doses of rosuvastatin. In most cases proteinuria returns to normal on its own without having to stop taking rosuvastatin tablets and is not associated with kidney problems.
Diabetes (diabetes mellitus)	Diabetes is common in the general population. Diabetes was reported for 1 in 10 to 1 in 100 patients in a major rosuvastatin clinical study. Patients are likely to be at risk of developing diabetes if they have high levels of sugars and fats in their blood, are overweight and have high blood pressure. Despite the risk of developing diabetes on statin treatment, the benefits still outweigh the risks.	The PIL informs patients that they will be monitored closely if they have diabetes or if they are at risk of developing diabetes. Prescribing information informs doctors that statins raise blood glucose and that some patients at a high risk of developing diabetes may need to be monitored with blood tests.
Low mood (depression)	Depression may affect people during rosuvastatin treatment, but the frequency is unknown. Depression affects people in different ways and can cause a wide variety of symptoms. They range from feelings of	The PIL informs patients about the risk of developing depression and that the frequency is unknown. Prescribing information informs doctors about the risk

Risk	What is known	Preventability
	<p>sadness and hopelessness, to losing interest in the things you used to enjoy and feeling very tearful. People with depression may also have symptoms of anxiety. Depression may cause other symptoms such as feeling constantly tired, sleeping badly, having no appetite or sex drive, and complaining of various aches and pains. The severity of the symptoms can vary. At its mildest, you may simply feel persistently low in spirit, while at its most severe depression can make you feel suicidal and that life is no longer worth living.</p>	<p>of developing depression and that the frequency is unknown.</p>
<p>Problems sleeping, nightmares (sleep disorders including insomnia and nightmares)</p>	<p>Sleep disorders may affect people during rosuvastatin treatment, but the frequency is unknown. Sleep disorders can lead to poor memory, depression, irritability, an increased risk of heart disease, and poor attention which increases the risk of accidents.</p>	<p>The PIL informs patients about the risk of developing sleep disorders. The PIL informs doctors about the risk of developing sleep disorders.</p>
<p>Muscle weakness caused by an autoimmune response (immune-mediated necrotising myopathy)</p>	<p>There have been rare reports of immune-mediated necrotizing myopathy in subjects using statins, including rosuvastatin. This is a condition in which the body's defense system against infections and other foreign material entering the body (the immune system) instead reacts to and attacks normal muscle tissue, which causes muscle damage, pain and weakness. This condition may persist after stopping the statin, and if</p>	<p>The PIL informs patients of the risk of muscle effects (see description in Skeletal muscle effects above). Prescribing information informs doctors of the reports of an immune-mediated necrotising myopathy with rosuvastatin, and its symptoms.</p>

Risk	What is known	Preventability
	so requires treatment with specific drugs to counteract the immunological reaction.	
Decreased number of platelets in the blood (thrombocytopenia/decreased platelet count)	A decrease in the number of platelets in the blood may occur during rosuvastatin treatment, but the frequency is unknown. People with thrombocytopenia may bleed or bruise easily.	Prescribing information informs doctors about the risk of developing low platelet count.
Severe skin reactions (Stevens-Johnson syndrome/ Toxic epidermal necrolysis)	Stevens-Johnson syndrome or toxic epidermal necrolysis may occur during rosuvastatin treatment but the frequency is unknown. Stevens-Johnson syndrome usually begins with fever, sore throat, and tiredness. Ulcers and other lesions begin to appear in the mucous membranes lining the mouth and lips but also in the genital and anal regions. Those in the mouth are usually extremely painful and reduce the patient's ability to eat or drink. Conjunctivitis (redness and soreness) of the eyes may also occur. A rash of round lesions about an inch (2-3cm) may spread across the face, trunk, arms and legs, and soles of the feet. The reaction may then develop into a more severe form with reddening of the skin with blisters or peeling. There may also be severe blisters and bleeding in the lips, eyes, mouth, nose and genitals. Toxic epidermal necrolysis is considered to be a more severe	The PIL informs patients about the risk of developing Stevens-Johnson syndrome. Prescribing information informs doctors about the risk of developing Stevens-Johnson syndrome.

Risk	What is known	Preventability
	form of Stevens-Johnson syndrome.	
Tendon disorders	Tendon disorders may occur during rosuvastatin treatment but the frequency is unknown. Patients with severe longstanding familial hypercholesterolaemia may be predisposed to tendon rupture due to tendon fragility. Other risk factors for tendon rupture include, but are not limited to, sports-related injury, increasing age, trauma, heavy lifting, strenuous activity, mechanical stress, and the use of medications associated with tendon rupture. Tendon rupture can cause significant disability.	The PIL informs patients and prescribing information informs doctors about the risk of developing tendon injury.
Damage to the nerves in hands and feet (peripheral neuropathy)	Peripheral neuropathy may occur during rosuvastatin treatment but the frequency is unknown. The nerve damage varies from mild tingling and altered sensation to irreversible disabling damage in the most severe cases. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy.	Prescribing information informs doctors about the risk of developing peripheral neuropathy.
Important identified drug-drug interactions: Ciclosporin (used, for example, after organ transplant to suppress the immune system) Various protease inhibitor combinations with ritonavir (used to fight HIV infection) Gemfibrozil (used to lower cholesterol) Clopidogrel (used for thinning the blood)	Drugs that increase the levels of rosuvastatin in the blood may increase the risk of side effects. Ciclosporin increases the levels of rosuvastatin in the blood by more than 7 times; rosuvastatin does not significantly affect ciclosporin levels in the blood.	The PIL instructs patients to tell their doctor to if they are taking any other medicines, including the following: ciclosporin (used for example, after organ transplants), warfarin or clopidogrel (or any other drug used for thinning the blood), fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to

Risk	What is known	Preventability
<p>Eltrombopag (used to treat abnormally low blood platelet counts) Dronedarone (used to treat cardiac arrhythmias) Warfarin and other vitamin K antagonists (or any other drug used for thinning the blood) Fusidic acid (used to treat bacterial infections) Ezetimibe (used to lower cholesterol)</p>	<p>Various protease inhibitor combinations with ritonavir increase rosuvastatin levels in the blood by 0 to 3.1 times, depending on the combinations.</p> <p>Gemfibrozil increases the level of rosuvastatin in the blood by 1.9 times.</p> <p>Clopidogrel increases the level of rosuvastatin in the blood by 2 times.</p> <p>Ezetimibe increases the levels of rosuvastatin in the blood by 1.2 times.</p> <p>Eltrombopag increases the levels of rosuvastatin in the blood by 1.6 times.</p> <p>Dronedarone increases the levels of rosuvastatin in the blood by 1.4 times.</p> <p>Warfarin levels are not affected by rosuvastatin, but as with other HMG-CoA reductase inhibitors, co-administration of rosuvastatin may result in a rise in INR (which tests how thin the blood is).</p> <p>Fusidic acid is predicted to increase the levels of rosuvastatin in the blood by up to 2.6 times.</p>	<p>lower cholesterol (such as ezetimibe), fusidic acid (an antibiotic), or ritonavir with lopinavir and/or atazanavir.</p> <p>Prescribing information informs doctors to adjust the dose according to the expected increase in exposure for patients taking one of these drugs at the same time as rosuvastatin. They are also advised that for patients taking warfarin or any other drug used for thinning the blood, monitoring of INR is recommended when starting, stopping or changing rosuvastatin therapy.</p> <p>Rosuvastatin should not be given to patients who are taking ciclosporin.</p>

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Kidney damage/failure (Renal failure (including acute and chronic renal failure) and renal impairment)	As the kidneys normally filter waste products from the blood, the symptoms of kidney damage are often related to the buildup of these waste products. The damage can be acute (may be able to be reversed by treating the underlying cause) or chronic (not reversible). Treatment usually requires dialysis, which involves filtering the waste products from the blood with a machine. There is insufficient evidence of a possible causal relationship between kidney damage/failure and rosuvastatin use, but this potential risk is monitored.
Liver failure (hepatic failure, including hepatic necrosis and fulminant hepatitis)	Liver failure occurs when large parts of the liver become damaged beyond repair and the liver is no longer able to function. It can be a serious condition that demands urgent medical care. Most often, liver failure occurs gradually and over many years. However, a more rare condition known as acute liver failure occurs rapidly (possibly in as little as 48 hours) and can be difficult to detect initially. There is insufficient evidence of a possible causal relationship between liver failure and rosuvastatin use, but this potential risk is monitored.
Progressive motor neuron disease (Amyotrophic lateral sclerosis)	Amyotrophic lateral sclerosis is a motor neuron disease characterised by progressive muscle weakness. Most people with amyotrophic lateral sclerosis die within 3 to 5 years of onset, usually because the muscles that control breathing are affected, leading to respiratory failure. There is no cure for amyotrophic lateral sclerosis. There is insufficient evidence of a possible causal relationship between amyotrophic lateral sclerosis and rosuvastatin use, but this potential risk is monitored.
Lung disease (Interstitial Lung Disease)	Interstitial Lung Disease is caused by inflammation in the space between the air sacs of the lungs and the blood vessels. Symptoms include shortness of breath, dry cough and deterioration in general health (fatigue, weight loss and fever). Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy.

Missing information

Risk	What is known
Children <6 years of age	The safety and efficacy of use in children younger than 6 years of age has not been studied.
Drug interactions: drug-drug interactions in paediatric population	Interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the national agency's internet page.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable. No postauthorisation studies are planned.

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

Not applicable. This is the first RMP.