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.

The effect of rosuvastatin on lipid levels in the blood was studied in an extensive clinical trial programme which included over 60,000 adults (more than 35,000 received rosuvastatin). A

separate 1-year trial was also completed in 176 children over 10 years of age who have familial hypercholesterolaemia, an inherited disease that causes high cholesterol levels from a relatively young age. Together, these studies showed that rosuvastatin lowers 'bad' cholesterol levels, raises 'good' cholesterol levels, and generally improves the amounts of lipids in the blood.

Rosuvastatin has also been compared to other statins. For example, the STELLAR trial showed that rosuvastatin more effectively lowered 'bad' cholesterol levels than similar doses of other statins.

To study whether rosuvastatin reduces the build-up of fatty deposits in blood vessels, the METEOR trial studied the effect of rosuvastatin on the thickness of blood vessel walls in the necks of 985 patients with moderately high cholesterol levels. Rosuvastatin treatment for 2 years slowed or delayed the thickening of the blood vessel wall caused by fatty deposits.

The ability of rosuvastatin to prevent death, stroke, heart attacks, and other related cardiovascular diseases was studied in the JUPITER trial. This trial included more than 17000 patients who had normal cholesterol levels, but who had other risk factors for developing cardiovascular disease. Rosuvastatin almost halved the number of cardiovascular-related deaths, stroke and heart attacks compared to placebo and reduced the total number of deaths by 20%.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of rosuvastatin in children younger than 6 years has not been established.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Muscle damage	It is a rare possible side effect which may affect between 1 in	Yes

Risk	What is known	Preventability
(Rhabdomyolysis)	1,000 and 1 in 10,000 patients. Muscle symptoms are more common in children and adolescents than in adults. 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.	Do not take Rosuvastatin if you have repeated or unexplained muscle aches or pains In addition, do not take Rosuvastatin (the highest dose) if you have had any 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. Stop taking rosuvastatin 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.
Muscle aches and pains as a symptom of a muscle damage (Myopathy, Myositis, Myalgia, CK increases, Myoglobinuria and Myoglobinaemia (in the setting of Rhabdomyolysis	It is a rare possible side effect which may affect between 1 in 1,000 and 1 in 10,000 patients. Rosuvastatin may cause repeated or unexplained muscle aches or pains. Rosuvastatin may cause in whom had any repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a previous history of	Yes Do not take Rosuvastatin if you have repeated or unexplained muscle aches or pains In addition, do not take Rosuvastatin (the highest dose) if you have had any repeated or unexplained muscle aches or pains, a personal or family history of muscle problems, or a

Risk	What is known	Preventability
and Myopathy)	muscle problems when taking other cholesterol-lowering medicines.	previous history of muscle problems when taking other cholesterol-lowering medicines. Stop taking rosuvastatin and tell your doctor immediately if you have unexplained muscle aches or pains especially if you feel unwell or have a fever. Also tell your doctor or pharmacist if you have a muscle weakness that is constant.
Increase in liver enzymes in the blood (Increased transaminases), Inflammation of liver (Hepatitis), Yellowing of the skin and eyes (Jaundice)	Increased transaminases are rare (between 1 in 10000 and 1 in 1000 patients) and jaundice and hepatitis are very rare (<1 in 10,000 patients) with rosuvastatin treatment.	Patients should not take rosuvastatin if they currently have a disease of 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 doctor may perform a simple blood test (liver function test) before and during rousvastatin treatment which looks for increased levels of liver enzymes in the blood.
Severe stomach pain – inflammation of the pancreas	It is a rare possible side effect which may affect between 1 in 1,000 and 1 in 10,000 patients.	On rare occasions, some people may develop a severe stomach pain (inflamed pancreas).

Risk	What is known	Preventability
(Pancreatitis)		
Memory loss	It is a very rare possible side effect which may affect less than 1 in 10,000 patients.	Very rarely a few people may suffer from memory loss while on rosuvastatin treatment.
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.	Yes 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 tablets
Serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome and Toxic epidermal necrolysis)	Frequency of occurrences of this possible side effect is unknown.	Serious blistering condition of the skin, mouth, eyes and genitals has been observed with Rosuvastatin.
High levels of sugars in blood (Diabetes mellitus)	It is a common possible side effect which may affect between 1 in 10 and 1 in 100 patients. Patients those are likely to be at risk of developing diabetes if they have high levels of sugars and fats in your blood, are overweight and have high blood pressure.	Yes While patient is on this medicine his/her doctor will monitor his/her closely if he/she has diabetes or is at risk of developing diabetes.

Risk	What is known	Preventability
Low mood (Depression)	Depression may affect people during rosuvastatin treatment, but the frequency is unknown. .	The PIL informs patients about the risk of developing depression and that the frequency is unknown.
Sleep disturbances, including insomnia and nightmares (Sleep disorders, including Insomnia and Nightmares)	Sleep disorders may affect people during Rosuvastatin treatment, but the frequency is unknown.	The PIL informs patients about the risk of developing sleep disorders.
Muscle weakness caused by an autoimmune response (Immune-mediated necrotising myopathy)	There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with 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 so requires treatment with specific drugs to counteract the immunological reaction.	The PIL informs patients of the risk of muscle effects
Decreased platelet count	It is a rare possible side effect which may affect between 1 in	Prescribing information informs doctors about the risk of

Risk	What is known	Preventability
(Thrombocytopenia)	1,000 and 1 in 10,000 patients.	developing low platelet count.
Tendon injury (Tendon disorders)	Tendon disorders may occur during rosuvastatin treatment but the frequency is unknown.	The PIL informs patients and prescribing information informs doctors about the risk of developing tendon injury.
Drug-drug interactions including, Ciclosporin, Various protease inhibitor combinations with Ritonavir, Gemfibrozil, Eltrombopag, Dronedarone, Itraconazole, Warfarin, Other Vitamin K antagonists and Ezetimibe.	Concomitant administration of these drugs is contradicted with rosuvastatin as they may result in increased rosuvastatin plasma concentrations and increases risk of muscle damage.	Yes Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including the following: • ciclosporin (used for example, after organ transplants). • warfarin (or any other drug used for thinning the blood). • fibrates (such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe). • indigestion remedies (used to neutralise acid in your stomach). • erythromycin (an antibiotic). • an oral contraceptive (the

Risk	What is known	Preventability
		pill). • hormone replacement therapy. • combinations of ritonavir with atazanavir, lopinavir, and/or tipranavir lopinavir/ritonavir (used to fight the HIV infection- please see Warnings and precautions). When it is necessary to co-administer rosuvastatin with these medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted accordingly.

Important potential risks

Risk	What is known
Kidney problems (Renal failure, including Acute and Chronic renal failure and Renal impairment)	Do not take if you have severe kidney problems. There is insufficient evidence of a possible causal relationship between kidney damage/failure and rosuvastatin use, but this potential risk is monitored.
Liver disease (Hepatic failure: including Hepatic necrosis and Fulminant	Do not take if you have liver disease. There is insufficient evidence of a possible causal relationship between liver failure and Rosuvastatin use, but

Risk	**What is known**
hepatitis)	this potential risk is monitored.
Damage to the nerves of legs and arms such as numbness (Peripheral neuropathy)	Peripheral neuropathy may occur during Rosuvastatin treatment but the frequency is very rare (1 in 10,000 people).
Build up of fatty deposits in arteries (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.
Interstitial lung disease	Exceptional cases of interstitial lung disease have been reported with some statins, especially with long term therapy. Presenting features can include shortness of breath, dry 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.
Drug-drug interaction with Fibrates (other than Gemfibrozil)	Statins and fibrates are each known to increase the risk of muscle problems. Therefore, the combination of the two types of drugs may increase the risk even further. Prescribing information informs doctors that the 40 mg dose should not be given to patients who have an increased risk of developing

Risk	What is known
	muscle problems, including patients taking fibrates.

Missing information

Risk	What is known
Liver disease (Severe hepatic impairment)	There is no experience in subjects with Severe liver impairment.
Elderly subjects	A start dose of 5 mg is recommended in patients >70 years. No other dose adjustment is necessary in relation to age.
Paediatric subjects	The safety and efficacy of use in children younger than 6 years has not been studied. Therefore, Rosuvastatin is not recommended for use in children younger than 6 years.
Kidney disease (Severe renal impairment)	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. The use of Rosuvastatin in patients with severe renal impairment is contraindicated for all doses.
Pregnant or Lactating women	Do not take rosuvastatin if you are pregnant or breast-feeding. If you become pregnant while taking rosuvastatin stop taking it immediately and tell your doctor. Women

Risk	What is known
	should avoid becoming pregnant while taking rosuvastatin by using suitable contraception. Rosuvastatin is excreted in the milk of rats. There are no data with respect to excretion in milk in humans.
Increased drug effect in Asian population (Asian population: Increased plasma exposure)	Increased blood levels of rosuvastatin have been seen in Asian subjects. The recommended start dose is 5 mg for patients of Asian ancestry. The 40 mg dose is contraindicated in these patients.
Very low bad cholesterol levels (Very low LDL-C levels)	Not known
Increased drug effect due to genetic variations (Genetic polymorphisms: Increased plasma exposure)	Specific types of genes are known that can lead to increased rosuvastatin exposure. For patients who are known to have such specific types of genes, a lower daily dose of Rosuvastatin is recommended.

VI.2.5 Summary of additional 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.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions can be found in Annex 10 and 11 of this RMP; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities. These additional risk minimisation measures are for the following risks:

Muscle effects and liver effects

Healthcare Professional education
Objective and rationale: To maximise the use of the appropriate start dose of rosuvastatin and to emphasise the appropriate approach to reach the maximum dose of rosuvastatin.
Proposed actions: • Communication to healthcare providers. • Review of rosuvastatin usage. • Restriction of samples. • Educational activities.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	**Date**	**Safety Concern**	**Comment**
3.0	26-May-2015	No changes were made to safety concerns.	RMP has been updated as per RMS Day 120 Assessment Report
2.0	20-Jan-2015	Safety concerns were updated to make them in line with the reference product: **Important identified risk:** • Rhabdomyolysis • Myopathy, myositis, myalgia,	RMP has been updated as per RMS Day 70 Assessment Report -Additional risk minimisation measures relating to the Muscle

		CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) • Increased transaminases, hepatitis, jaundice • Pancreatitis • Memory Loss • Proteinuria • Stevens-Johnson syndrome and Toxic epidermal necrolysis • Diabetes mellitus • Depression • Sleep disorders (including insomnia and nightmares) • Immune-mediated necrotising myopathy • Thrombocytopenia/decreased platelet count • Tendon disorders • Drug-drug interactions including, ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and	effects and liver effects safety concerns, including Review of rosuvastatin usage, Restriction of samples and Educational activities • Part VI have been updated accordingly

		ezetimibe **Important potential risk:** • Renal failure (including acute and chronic renal failure) and renal impairment • Hepatic failure: including hepatic necrosis and fulminant hepatitis • Peripheral neuropathy • Amyotrophic lateral sclerosis • Interstitial lung disease • Drug-drug interaction with fibrates (other than gemfibrozil) **<u>Missing information:</u>** • <u>Severe hepatic impairment</u> • <u>Elderly subjects</u> • <u>Paediatric subjects</u> • <u>Severe renal impairment</u> • <u>Pregnant or lactating women</u> • <u>Asian population: increased plasma exposure</u> • <u>Very low LDL-C levels</u> • <u>Genetic polymorphisms: increased plasma exposure</u>	