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 are the world's biggest killers, claiming more than 17 million lives each year worldwide.

Globally, a third of ischaemic heart disease is attributable to high cholesterol. In 2008 the global prevalence of raised total cholesterol among adults (≥ 5.0 mmol/l) was 39%. The prevalence of raised total cholesterol increased noticeably according to the income level of the country. In low income countries around a quarter of adults had raised total cholesterol, in lower middle income countries this rose to around a third of the population for both sexes. In high-income countries, over 50% of adults had raised total cholesterol; more than double the level of the low-income countries.

A 10% reduction in serum cholesterol in men aged 40 has been reported to result in a 50% reduction in heart disease within 5 years. 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 old, 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 like atorvastatin, simvastatin or pravastatin.
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

There is limited information available for rosuvastatin use in children < 6 years of age and drug-drug interaction studies in the paediatric population. Experience in children with homozygous familial hypercholesterolaemia is limited to a small number of children aged between 8 and 17 years.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Abnormal muscle breakdown which can lead to kidney problems (rhabdomyolysis)	As with other cholesterol lowering medicines, 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. Rhabdomyolysis are rare (between 1 in 10,000 and 1 in 1,000 patients). This has been reported in rosuvastatin-treated patients with all doses, and in particular with doses more than 20 mg rosuvastatin.	Patients should inform to the doctor or pharmacist before taking rosuvastatin when he/she has 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. The patient should tell the doctor immediately if he/she has unexplained muscle aches or pains especially if he/she feels unwell or have a fever. Also he/she should tell the doctor or pharmacist if he/she has a muscle weakness that is constant. Rosuvastatin should be stopped and medical help should be sought immediately if any

		unusual aches or pains in muscles last longer than expected.
Muscle weakness, aches and pain (myopathy, myositis and myalgia), Creatine kinase (an enzyme released by damaged muscles) elevation , presence of myoglobin in blood and urine (myoglobinuria and myoglobinaemia)	As with other cholesterol lowering medicines, a very small number of people have experienced unpleasant muscle effects. Rosuvastatin may cause repeated or unexplained muscle aches or pains. Muscle pain is common (between 1 in 100 and 1 in 10 patients); muscle weakness (myopathy including myositis) is a rare possible side effect which may affect between 1 in 1,000 and 1 in 10,000 patients.	Patients should inform to the doctor or pharmacist before taking rosuvastatin when he/she has 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. The patient should tell the doctor immediately if he/she has unexplained muscle aches or pains especially if he/she feels unwell or have a fever. Also he/she should tell the doctor or pharmacist if he/she has a muscle weakness that is constant. Rosuvastatin should be stopped and medical help should be sought immediately if any unusual aches or pains in muscles last longer than expected.
Elevated liver enzymes (Increased transaminases); inflammation of liver (Hepatitis); yellowing of the skin and white of the eyes (Jaundice)	In a small number of people, statins can affect the liver. This is identified by a simple test which looks for increased levels of liver enzymes in the blood. Increases in liver enzymes in the blood occur rarely (may affect up to 1 in 1,000 people), hepatitis (an inflamed liver) and jaundice are very rare (may affect up to 1 in 10,000 people).	The patient should talk to his/her doctor or pharmacist before taking rosuvastatin when he/she has problems with his/her liver. Patients with a liver disease should not take rosuvastatin. Doctor should usually carry out blood test (liver function test) before and during treatment with rosuvastatin.
Inflammation of the pancreas (pancreatitis)	Inflammation of the pancreas (pancreatitis) is rare (between 1 in 10000 and 1 in 1000 patients) with rosuvastatin treatment.	Prescribing information informs doctors that pancreatitis occurs rarely in patients taking rosuvastatin. Patient should be informed to report to the treating physician if he/she suffers from pancreatitis during treatment with rosuvastatin.
Memory loss	Memory loss is very rare (less than 1 in 10,000 patients) with	Prescribing information informs doctors that memory loss can

	rosuvastatin treatment.	occur in patients treated with rosuvastatin. Patient should be informed to report to the treating physician if he/she has loss of memory during treatment with rosuvastatin.
An increase in the amount of protein in the urine (proteinuria)	Patients treated with higher doses of rosuvastatin (in particular rosuvastatin 40 mg) are likely to develope an increase in the amount of protein in the urine. This usually returns to normal on its own without having to stop taking Rosuvastatin.	Prescribing information informs doctors that it is recommended to carry out a routine urine test to detect proteinuria during the follow up of patients on highest dose of rosuvastatin.
Disease with high blood sugar values (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 his blood, are overweight and have high blood pressure. Despite the risk of developing diabetes on statin treatment, the benefits still outweigh the risk.	Prescribing information informs that patients with diabetes or at risk of developing diabetes should be monitored closely. Doctors should monitor these patients according to national guidelines while taking rosuvastatin.
Depression	Cases of depression have been observed with use of rosuvastatin however the frequency is not known.	Prescribing information informs doctors about the risk of developing depression and that the frequency is unknown.
Sleep disorders (including insomnia and nightmares)	Cases of sleep disturbances have been observed with use of rosuvastatin however the frequency is not known.	This risk is stated in the product information.
Muscle weakness caused by an autoimmune response (Immune-mediated necrotising myopathy-IMNM)	There have been very rare reports of an immune-mediated necrotising myopathy (IMNM) during or after treatment with statins, including rosuvastatin, however the frequency is not known. IMNM is clinically characterized by proximal muscle weakness and elevated serum creatine kinase which persist despite discontinuation of statin treatment.	Doctors should carry out a blood test for measure the Creatinine kinase levels (CK) during treatment with rosuvastatin and stopping the treatment if this condition occurs.

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.	This risk is stated in the product information.
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.	These risks are stated in the product information.
Tendon injury (tendon disorders)	The side effects from rosuvastatin use related to tendon injury (tendon disorders) have been reported with other statins.	This risk is stated in the product information.
Damage to the nerves in hands and feet (peripheral neuropathy)	Peripheral neuropathy may occur during rosuvastatin treatment but the frequency is unknown.	This risk is stated in the product information.
Drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, simeprevir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin and other vitamin K antagonists, fusidic acid, and ezetimibe.	Drugs that increase the levels of rosuvastatin in the blood may increase the risk of side effects. The risk of muscle damage is increased when rosuvastatin is administered together with certain medicinal products as ciclosporin (used for example, after organ transplants), warfarin (or any other drug used for thinning the blood), fibrates (other king of drugs used to control the cholesterol, such as gemfibrozil, fenofibrate) or any other medicine used to lower cholesterol (such as ezetimibe), fusidic acid (an antibiotic), hormone replacement therapy or ritonavir with lopinavir and/or atazanavir (used to treat the HIV infection). Concomitant use with ciclosporin is contraindicated.	As stated in the patient leaflet, patients should tell their doctor if they are taking any other medicines, including ciclosporin; warfarin or clopidogrel (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); fusidic acid (an antibiotic), or ritonavir with lopinavir and/or atazanavir. Whenever possible, alternative medications should be considered and, if necessary consider rosuvastatin dosing adjustments or temporarily discontinuing rosuvastatin treatment.

Important potential risks

Risk	What is known
Renal failure (including acute and chronic renal failure)	Increased amount of protein in the urine has been reported in patients treated with rosuvastatin. Review of data from clinical trials and post-marketing experience to date has not identified a

and renal impairment.	relation between increase amount of protein in the urine and loss of kidney function. In patients with moderate renal impairment, the lowest dose (rosuvastatin 5 mg) may be started. Use of rosuvastatin in patients with severe renal impairment is not recommended at any dose.
Liver/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. Patients with severe liver disease are at risk of increased blood levels of rosuvastatin during treatment. Carrying out blood test (liver function test) during treatment with rosuvastatin is recommended.
Progressive motor neuron disease (ALS)	Amyotrophic lateral sclerosis is a motor neuron disease characterised by progressive muscle weakness. Exceptional cases of serious brain and muscle disorder like amyotrophic lateral sclerosis are reported and in such cases it is recommended to stop taking the drug. However, some publications have not established a clear relationship between the administration of statins and the development of ALS.
Lung disease (Interstitial lung disease-ILD)	Interstitial lung disease is caused by inflammation in the space between the air sacs of the lungs and the blood vessels. Exceptional cases of interstitial lung disease have been reported with some statins, especially with long-term therapy. Symptoms 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.
Drug interactions: Fibrates (other than gemfibrozil)	Fenofibrate, ezetemibe, other fibrates and niacin (nicotinic acid) increase the risk of muscle pain or weakness when given together with rosuvastatin, probably because they can produce muscle pain or weakness when given alone.

Missing information

Risk	What is known
Children <6 years of age	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.
Drug-drug interaction studies in the paediatric population	Drug-drug 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.
This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

No post-authorisation studies are planned and therefore this section is not applicable.

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

Not applicable, since this is the first RMP of rosuvastatin.