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, things that cannot be changed, such as age, sex, or family medical history often affect cholesterol levels. Cholesterol levels usually rise steadily with age, but stabilise after middle age. Approximately 1 in 500 people have an inherited disease called familial hypercholesterolemia, 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.

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 Unknown relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

However, there is minimal information on the efficacy and safety of treatment of paediatric patients under the age of 6 years and drug-drug interaction studies in the paediatric population.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Muscle-damage (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	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

Risk	What is known	Preventability
	rhabdomyolysis. Rhabdomyolysis are rare (may affect up to 1 in 1,000 people). This has been reported in rosuvastatin-treated patients with all doses, and in particular with doses more than 20 mg rosuvastatin.	problems when taking other cholesterol-lowering medicines. Patients should not 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.
Muscle disease which results in muscular weakness (myopathy), inflammation or swelling of the muscles (myositis), muscle aches (myalgia), creatine kinase (an enzyme released by damaged muscles) elevation, presence of myoglobin in urine and blood (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 (may affect up to 1 in 10 people); 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	Treatment with the highest possible dose (40mg) of rosuvastatin is not allowed in patients at risk of muscle disease. 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.
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	The PIL instructs patients not to 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

Risk	What is known	Preventability
	inflamed liver) and jaundice are very rare (may affect up to 1 in 10,000 people).	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 (may affect up to 1 in 1,000 people) with rosuvastatin treatment.	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 (may affect up to 1 in 10,000 people) with rosuvastatin treatment.	The PIL informs patients that very rarely a few people may suffer from memory loss while on rosuvastatin treatment. Prescribing information informs doctors that memory loss occurs very rarely in patients taking rosuvastatin.
An increase in the amount of protein in the urine (proteinuria)	Patients treated with higher doses of rosuvastatin (in particular 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.	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 in patients taking higher doses of rosuvastatin. In most cases,

Risk	What is known	Preventability
		proteinuria returns to normal on its own without having to stop taking rosuvastatin tablets and is not associated with kidney problems.
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 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)	Cases of depression have been observed with use of rosuvastatin however, the frequency is not known.	The PIL informs patients about the risk of developing depression and that the frequency is unknown. Prescribing information informs doctors about the risk of developing depression and that the frequency is unknown
Problems sleeping (sleep disorders, including insomnia and nightmares)	Cases of sleep disturbances have been observed with use of rosuvastatin however the frequency is not known.	The PIL informs patients about the risk of developing sleep disorders. Prescribing information informs doctors about the risk of developing sleep disorders
Muscle weakness caused by an autoimmune response (Immune Mediated Necrotising Myopathy)	There have been rare reports of immune-mediated necrotizing myopathy in subjects using statins, including rosuvastatin. 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 (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.
Decreased number of	A decrease in the number of	Prescribing information

Risk	What is known	Preventability
platelets in the blood (thrombocytopenia/ decreased platelet count)	platelets in the blood may occur during rosuvastatin treatment, but the frequency is unknown. People with thrombocytopenia may bleed or bruise easily.	informs doctors about the risk of developing low platelet count.
Severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)	Stevens-Johnson syndrome or toxic epidermal necrolysis may occur during rosuvastatin treatment but the frequency is unknown.	The PIL informs patients about the risk of developing severe skin reactions. Prescribing information informs doctors about the risk of developing Stevens-Johnson syndrome and toxic epidermal necrolysis.
Tendon injury (tendon disorders)	The side effects from rosuvastatin use related to tendon injury (tendon disorders) have been reported with other statins.	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.	Prescribing information informs doctors about the risk of developing peripheral neuropathy.
Drug-drug interactions including ciclosporin, various protease inhibitor combinations with ritonavir, clopidrogrel, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, fusidic acid, ezetimibe and simeprevir	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	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

Risk	What is known	Preventability
	and/or atazanavir (used to treat the HIV infection). Concomitant use with ciclosporin is contraindicated.	treatment.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Renal failure (including acute and chronic renal failure) and renal impairment	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 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 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
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. 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.
Progressive motor neuron disease (Amyotrophic lateral sclerosis)	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.
Drug-drug interactions with 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 activities 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.

No additional risk minimisation activities are required. Routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

VI.2.6 Planned post-authorisation development plan

There are no studies in the post authorisation development plan.

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

Not applicable