VI.2 Elements for a Public Summary

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).People with high blood cholesterol levels have a greater risk of having a heart attack, stroke or other related cardiovascular disease. Cardiovascular diseases such as strokes and heart attacks cause almost 1 in 3 deaths worldwide each year.
Cholesterol levels usually rise steadily with age, but stabilize after middle age. Approximately 1 in 500 people have an inherited disease called familial hypercholesterolaemia, which causes very high cholesterol levels even during childhood. In 2010, just over 13% of population in the US had high total cholesterol levels.

Cardiovascular disease 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 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 trialprogramme 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%.[1]

Rosuvastatin Aurobind is a generic medicine that is given orally and contains the same active substance as the reference medicine.

Because rosuvastatin Aurobindo is a generic, its beneficial treatment effects are taken as being the same as the reference medicines.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of use in children younger than 6 years of age has not been studied.

VI.2.4 Summary of safety concernsImportant identified risks

Risk	What is known	Preventability
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).	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.	The 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 rosvustatin if they have repeated or unexplained muscleaches or pains.
Increased levels of liver enzymes in the blood (increased transaminases), liver inflammation (hepatitis), yellowing of 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. 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 isexposed to	The patients not to take rosuvastatin if they currently have a disease of their liver. Before taking the rosuvastatin, patients should tell their doctor or pharmacist if they have any problems with their liver or

[1] CRESTOR™, rosuvastatin calcium Version Number of EU-RMP when last updated 3 Data lock point for this module 30 June 2014

Risk	What is known	Preventability
	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.	regularly drink large amounts of alcohol. Carrying out this blood test (liver function test) before and during treatment with rosuvastatin.
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.	Rosuvastatin 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. 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.
Difficulty remembering things (Memory loss)	Memory loss is very rare (less than 1 in 10,000 patients) with rosuvastatin treatment.	Talk to your doctor or pharmacist if you notice yourself becoming more forgetful during treatment with 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.	An increased protein level in your urine can be discovered during a urine test. Your doctor will advise

Risk	What is known	Preventability
		you on the best course of action. 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 reaction
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.	Your doctor will monitor you closely if you have diabetes or are at risk of developing diabetes. If you get any side effects, talk to your doctor or Pharmacist.
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 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	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

Risk	What is known	Preventability
	suicidal and that life is no longer worth living.	
Problems sleeping, nightmares (Sleep disorders including insomnia and nightmares)	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.	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 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 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.	Rosuvastatin should be stopped and medical help should be sought immediately if any unusual aches or pains in muscles last longer than expected
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.	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.

Risk	What is known	Preventability
		This will minimise the risk of developing adverse drug reactions
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 form of Stevens-Johnson syndrome.	If you notice blistering of your skin, mouth or genitals, immediately stop taking rosuvastatin and consult a
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.	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

Risk	What is known	Preventability
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.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the package leaflet.
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) Eltrombopag (used to treat abnormally low blood platelet counts) Dronedarone (used to treat cardiac arrhythmias) Warfarin (or any other drug used for thinning the blood) Fusidic acid (used to treat bacterial infections) Ezetimibe (used to lower cholesterol)	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. Various protease inhibitor combinations with ritonavir increase rosuvastatin levels in the blood by 0 to 3.1 times, depending on the combinations. Gemfibrozil increases the level of rosuvastatin in the blood by 1.9 times. Clopidogrel increases the level of rosuvastatin in the blood by 2 times. Ezetimibe increases the levels of rosuvastatin in the blood by 1.2 times. Eltrombopag increases the levels of rosuvastatin in the blood by 1.6 times. Dronedarone increases the levels of rosuvastatin in the blood by 1.4 times. 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). Fusidic acid is predicted to increase the levels of rosuvastatin in the blood by up to 2.6 times.	Do not take rosuvastatin if you take a medicine containing a substance called ciclosporin (used, for example, after organ transplants). Do not take rosuvastatin 40 mg tablets if you take other medicines called fibrates to lower your cholesterol. Dose adjustment may be necessary if rosuvastatin is used with other drugs that affect the rosuvastatin blood level
Use during pregnancy and breast-feeding	Rosuvastatin may cause harm to the foetus/child if it is used during pregnancy/breast feeding	Rosuvastatin must not be used in pregnant and breastfeeding woman. Women should avoid becoming pregnant while taking rosuvastatin by using suitable contraception

Risk	What is known	Preventability
Use in Asian patients	Asian patients have higher drug blood concentrations than other populations. Because of this these patients are more prone to developing adverse events associated with rosuvastatin use	The lowest initial dose should be used in Asian patients. 40 mg tablets are contraindicated in this population

Important potential risks

Risk	What is known
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.
Important potential drug-drug interactions:fibrates other than gemfibrozil (used to lower cholesterol)	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 muscle problems, including patients taking fibrates.

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-drug interaction studies in the paediatric population	DDI studies in the paediatric population have not been performed.

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.
The Summary of Product Characteristics and the Package leaflet for rosuvastatin Aurobindo can be found in the national authority's web page.

VI.2.6 Planned post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation
None

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	23 January 2015	Children younger than 10 years	As per the INFARMED suggestion, the paediatric text has been removed.
3.0	05 Novemeber 2015	Important identified risks Inflammation of pancreas changed to pancreatitis Inceased amount of protein in urine changed to proteinuria Abnormal muscle breakdown which can lead to kidney problems (Rhabdomyolysis) Chnaged to Rhabdomyolysis	V 2.0 RMP has been updated in response to assessor commnets under PT/H/1419/001-004/DC

Version	Date	Safety Concerns	Comment
4.0	25 August 2016	Important identified risks Rhabdomyolysis modified as Rhabdomyolysis, and other muscle problems such as myopathy, myositis, 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). - Elevated liver enzymes, inflammation of the liver hepatitis, jaundice modified as Increased transaminases , (hepatitis), jaundice Diabetes modified as Diabetes mellitus - Sleep disturbances modified as sleep disorders including insomnia and nightmares. - Muscle damage (Immune-mediated necrotising myopathy) modified as Immune-mediated necrotising myopathy - Stevens-Johnson syndrome/ toxic epidermal necrolysis (serious blistering condition of the skin, mouth, eyes and genitals) modified as Severe skin reactions Stevens-Johnson syndrome/ toxic epidermal necrolysis -Tendon injury modified as Tendon disorder. - Disorder of the nerves (peripheral neuropathy) modified as peripheral neuropathy - Drug interaction including ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists and ezemtimibe modified as Drug interaction including	V3.0 RMP has been updated in response to assessor comments under DCP - PT/H/0689/001-004/DC-RUP procedure from Sweden

Version	Date	Safety Concerns	Comment
		ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, warfarin, Fusidic acid and ezemtimibe **Addition** Thrombocytopenia/decreased platelet count. **Deletion** -Use in subjects with liver disorders -Use in elderly patients -Use in subjects with kidney disorders -Use in Asian patients **Important Potential risks** **Addition** Renal failure (including acute and chronic renal failure) and renal impairment -Hepatic failure, including hepatic necrosis and fulminant hepatitis -Amyotrophic lateral sclerosis Modification Drug-drug interactions with fibrates other than gemfibrozil modified as Drug-drug interactions with fibrates other than gemfibrozil used to lower cholesterol) Deletion Loss of kidney function **Missing information** **Deletion** - Use in children under 10 years Addition Children <6 years of age Drug-drug interaction studies in the paediatric populatio	