VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

Familial hypercholesterolemia is an inherited disease that causes high cholesterol levels from a relatively young age. Heterozygous familiar hypercholesteremia refers to patients with one abnormal copy of the LDLR (low-density lipoprotein receptor) gene. These patients may have premature cardiovascular disease at the age of 30 to 40 years. When both copies of the gene are abnormal (homozygous), severe cardiovascular disease can occur in childhood.

Hyperlipidaemia is the term used for high levels of one or more of total cholesterol (TChol), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), or both TChol and TG (combined hyperlipidaemia). Combined hyperlipidaemia is often accompanied by decreased high-density protein cholesterol (HDL). Many types of hyperlipidaemia carry an increased risk of cardiovascular disease. Hyperlipidaemia is important as one of the three main modifiable risk factors for CVD (the others being smoking and hypertension).

•The UK population has one of the highest average serum cholesterol levels in the world.
•Two thirds of the UK population have a serum cholesterol level greater than 5.2 mmol/L.
•Low levels of High Density Cholesterol are often associated with increased triglycerides levels (e.g., in familial combined hyperlipidaemia and in dyslipidaemia in type 2 diabetes).
•Heterozygous familial hypercholesterolaemia is one of the most common familial conditions, with a prevalence of about 1 in 500, however less than 1% of these patients are diagnosed in most countries. Homozygous familial hypercholesterolaemia on the other hand is a are condition.

<u>Prevention of Cardiovascular Events</u>

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world. The underlying pathology is atherosclerosis, the thickening and hardening of arterial walls, which develops over many years. When symptoms occur, generally during middle age, the disease is usually advanced. Acute coronary events (heart attacks) and cerebrovascular events (strokes) often occur suddenly, and are often fatal before medical care can be given. By reducing the risk factor, these events and early death can be reduced in people who already have cardiovascular disease and also people who are at a high risk for this type of diseases due to one or more risk factors

VI.2.2 Summary of treatment benefits

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and also specific patient groups such as diabetics, or patients with familial hypercholesterolaemia.

Studies have shown that rosuvastatin is effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia

In a large study, 435 patients with heterozygous familial hypercholesterolaemia were given rosuvastatin from 20 mg to 80 mg.. For all doses, there was a beneficial effect on lipid parameters and treatment to target goals. After 12 weeks of treatment, when the patients were on a daily dose of 40 mg., the Low Density Lipoprotein-Cholesterol was reduced by 53%. 33% of patients reached the guidelines for LDL-C levels as provided by the European Atherosclerosis Society (<3 mmol/l).

In another study, 42 patients with homozygous familial hypercholesterolaemia were evaluated for their response to rosuvastatin 20 - 40 mg. In the overall population, the mean LDL-C reduction was 22%.

In clinical studies with a limited number of patients, rosuvastatin has been shown to have and additional effect in lowering triglycerides when used in combination with fenofibrate and in increasing HDL-C levels when used in combination with niacin.

VI.2.3 Unknowns relating to treatment benefits

There is limited information available for rosavastatin use in the paediatric population and in breastfeeding women. No clinical trial data is available for rosuvastatin use in children under the age of 6, furthermore there is limited trial data available regarding paediatric use in children aged 6 to 17 years old. Experience in children with homozygous familial hypercholesterolaemia is limited to a small number of children aged between 8 and 17 years. Rosuvastatin should not be used during breast feeding.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Rhabdomyolysis and myopathy: myositis, myalgia; CK increased; myoglobunuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy)	As with other statins, unpleasant muscle effects rarely have gone on to become a potentially life threatening muscle damage known as rhabdomyolysis. A dose-related increase in CK levels has been observed in patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient. If CK levels are elevated (>5xULN), treatment should be discontinued.	Rosuvastatin should be prescribed with caution in patients who have a higher risk of developing muscle problems. The patient should talk to his/her doctor or pharmacist before taking rosuvastatin when the patient 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. Whilst on treatment 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. CK levels should be measured in these patients. Also, the patients should stop taking rosuvastatin and talk to their doctor immediately if they have any unusual aches or pains in the muscles which go on for longer than one might expect.
Increased transaminases, hepatitis, jaundice	As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild, asymptomatic and transient.	Rosuvastatin should not be used in patients with active liver disease including unexplained, persistent elevations of serum transaminases and any serum transaminase elevation exceeding 3 x the upper limit of normal (ULN). 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 alcohol. Prescribing information informs doctors that rosuvastatin should not be used in patients with active liver disease or with elevated liver enzymes.
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 causes by drugs.	Both the PIL and the prescribing information inform about the risk of pancreatitis.
Memory loss	Memory loss has been reported with very rare frequency	Both the PIL and the prescribing information inform about the risk of memory loss.
Proteinuria	Proteinuria has been observed in patients treated with rosuvastatin, especially with higher doses. Although	Both the PIL and the prescribing information inform about the risk of proteinuria

	proteinuria can be a sign of kidney damage, in most cases it returns to normal on its own.	
Diabetes mellitus	The following adverse events have been reported with rosuvastatin: Diabetes mellitus, with frequency common; This is more likely if the patient has high levels of sugars and fats in his/her blood, is overweight and has high blood pressure.	Both the PIL and the prescribing information inform about the risk of diabetes mellitus. The doctor will monitor the patient while he/she is taking this medicine.
Depression	Depression with unknown frequency. Depression can cause various symptoms, including feelings of sadness and hopelessness and the loss of interested in things that were enjoyed before. Additional symptoms may include anxiety, tiredness and sleeping disorders, and loss of sex drive. In its mildest form, depression expresses itself as a persistent depressed mood, the most severe form includes feelings of suicide	Both the PIL and the prescribing information inform about the risk of depression.
Sleep disorders (including insomnia and nightmares)	Sleep disorders (including insomnia and nightmares) may be caused by various reasons, including stress, life style and day-night rhythm as well as medication. Sleeping disorders itself may cause other symptoms including memory problems, depression, attention disorders and agitation.	Both the PIL and the prescribing information inform about the risk of sleep disorders.
Immune mediated necrotizing myopathy (IMNM)	Immune mediated necrotizing myopathy (IMNM) has been reported with unknown frequency. This is a condition in which the body's immune system (the body's defense system, normally working against infections and other foreign material entering the body), reacts to and attacks normal muscle tissue. This can cause muscle damage, muscle weakness. This condition may	Both the PIL and the prescribing information inform about the risk of Immune mediated necrotizing myopathy (IMNM).

	persist after stopping the treatment with rosuvastatin and may require additional medical treatment to undo this reaction.	
Thrombocytopenia/decreased platelet count	Thrombocytopenia/decreased platelet count is reported with rosuvastatin with rare frequency. This can be detected via blood tests. People with thrombocytopenia (decreased platelet count) may bleed easily.	Both the PIL and the prescribing information inform about the risk of Thrombocytopenia/decreased platelet count.
Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN)	The following adverse events have been reported with rosuvastatin: Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) with unknown frequency. 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 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 blisters or peeling of the skin. Toxic epidermal necrolysis is considered to be a more severe form of Stevens-Johnson Syndrome.	Both the PIL and the prescribing information inform about the risk of Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN).
Tendon disorders	Tendon disorders have been reported with unknown frequency. Patients with severe longstanding familial hypercholesterolemia may be predisposed to tendon rupture due to tendon fragility. Other	Both the PIL and the prescribing information inform about the risk of tendon disorders.

	risk factors for tendon rupture include, but are not limited to, sport-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.	
Peripheral neuropathy	Peripheral neuropathy has been reported with unknown frequency. 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.	Both the PIL and the prescribing information inform about the risk of peripheral neuropathy.
Drug interactions: various protease inhibitor combinations with ritonavir, simeprevir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, fusidic acid and ezetimibe	Concomitant use of certain protease inhibitors are not recommended unless the dose of rosuvastatin is adjusted. The combination of rosuvastatin and gemfibrozil is not recommended. Caution should be used in the combined use of rosuvastatin and ezetimibe. 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 levels of rosuvastatin in the blood by 1.9 times; ezetimibe by 1.2 times, eltrombopag by 1.6 times, dronedarone by 1.4 times. Fusidic acid is predicted to increase the levels of rosuvastatin in the blood up to 2.6 times.	The PIL instructs patients to tell their doctor if they are taking any other medicines, including the following: ciclosporin (used for example, after organ transplants), warfarin or clopidogrel (or any other drug uses for thinning the blood), fibrates (such as gemfibrozil, fenofibrate) or any other medicine to lower cholesterol (such as ezetimibe), fusidic acid (an antibiotic), or ritonavir with lopinavir and/or atazanavir. 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.
Drug interactions: ciclosporin	Rosuvastatin should not be used by patients also receiving the medication ciclosporin. Ciclosporin increases the levels of rosuvastatin in the blood by more than 7 times.	The PIL instructs patients to tell their doctor if they are taking ciclosporin. Prescribing information informs doctor not to give Rosuvastatin to patients who are taking ciclosporin.
Drug interactions: warfarin and other vitamin K antagonists	When rosuvastatin is used concomitantly with Vitamin K antagonists like the medication warfarin or another coumarin anticoagulant) may result in an increase in International Normalised Ratio (INR): the time blood takes to clot. Discontinuation or down-titration of rosuvastatin may result in a decrease in INR. In such situations, appropriate monitoring of INR is desirable.	The PIL instructs patients to tell their doctor if they are taking warfarin or other vitamin K antagonists. Prescribing information informs doctor about the possible necessity to discontinue or down-titrate the Rosuvastatin treatment.

Important potential risks

Risk	What is known
Hepatic failure: including hepatic necrosis and fulminant hepatitis	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. For this reason, the doctor will usually carry out this blood test (liver function test) before and during treatment with rosuvastatin. Increases in liver enzymes in the blood occur rarely (may affect up to 1 in 1,000 people) and hepatitis (an inflamed liver) is 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.
Renal failure (including acute and chronic renal failure) and renal impairment	The patient should talk to his/her doctor or pharmacist before taking rosuvastatin when he/she has problems with his/her kidneys. Patients with severe kidney problems should not take rosuvastatin. As the kidneys normally filter waste products from the blood, the symptoms of kidneys 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).
Amytrophic lateral	Amyotrophic lateral sclerosis is a motor neuron disease characterised

sclerosis (ALS)	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 (ILD)	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.
Drug interactions: Fibrates (other than gemfibrozil)	The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated for patients who have an increased risk of developing muscle problems, including patients taking fibrates. 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.

Missing information

Risk	What is known
Use in 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.
DDI studies in the paediatric population	Drug-drug interaction 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.

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.

Part VII: Annexes

Annex 1 – Interface between RMP and Eudravigilance

Not applicable, as this is only required for centrally authorized products.