VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of rosuvastatin has been established.

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 clinical trial programme included a broad range of individuals. Most of the patients/subjects were adult Caucasians (Whites). There is no evidence to suggest that results would be different in non-Caucasians. In children 6 to 17 years of age, the long-term safety and tolerability of rosuvastatin have been studied for up to 2 years. The safety and efficacy of use in children younger than 6 years of age has not been studied.

VI: 2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and missing information, these are defined as follows:

An important identified risk is an untoward event for which there is enough evidence for it to be linked with the medicine of interest, and where the possibility of that event occurring could lessen the potential benefits of taking the medicine.

An important potential risk is an untoward occurrence for which there is some reason for suspicion of a link with the medicine of interest but where this link has not been confirmed.

Missing information is information about the safety of a medicine which is not available when the medicine was approved for sale. This may represent a gap in the ability to predict the safety of the medicine on particular topics after the medicine has been approved.

Table VI-4 Important 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 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 problems when taking other cholesterol-lowering medicines. Patients should not to take rosvustatin 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.

Table VI-4 Important identified risks

Risk	What is known	Preventability
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 is exposed to 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.	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. The PIL also informs patients that 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. 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 (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.	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.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Difficulty remembering things (memory loss)	Memory loss is very rare (less than 1 in 10,000 patients) 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)	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.	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 patients taking higher doses of rosuvastatin. In most cases proteinuria returns to normal on its own without having to stop taking rosuvastatin tablets and is not associated with kidney problems.
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.	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.

Table VI-4 Important identified risks

Risk	What is known	Preventability
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 suicidal and that life is no longer worth living.	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, 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.	The PIL informs patients about the risk of developing sleep disorders. The PIL informs doctors about the risk of developing sleep disorders.

Table VI-4 Important identified risks

Risk	What is known	Preventability
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.	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 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.	Prescribing information informs doctors about the risk of developing low platelet count.

Table VI-4 Important identified risks

Risk	What is known	Preventability
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.	The PIL informs patients about the risk of developing Stevens-Johnson syndrome. Prescribing information informs doctors about the risk of developing Stevens-Johnson syndrome.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Tendon disorders	Tendon disorders may occur during rosuvastatin treatment but the frequency is unknown. Patients with severe long-standing 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.	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. 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.	Prescribing information informs doctors about the risk of developing peripheral neuropathy.

Table VI-4 Important identified risks

Risk	What is known	Preventability
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.	The PIL instructs patients to tell their doctor to if they are taking any other medicines, including the following: ciclosporin (used for example, after organ transplants), 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. 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. Rosuvastatin should not be given to patients who are taking ciclosporin.

HIV Human immunodeficiency virus; HMG-CoA 3-hydroxy-3-methylglutaryl coenzyme A; INR International normalised ratio; PIL Patient information leaflet.

Table VI-5 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
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.

Table VI-5 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
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.

Table VI-6 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.
DDI studies in the paediatric population	DDI studies in the paediatric population have not been performed.

BMI Body Mass Index; DDI Drug-drug interaction

VI: 2.5 Summary of additional risk minimisation measures by safety concern

Table VI-7 Muscle effects and liver effects

Risk minimisation measure(s)
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.

Table VI-7 Muscle effects and liver effects

Risk minimisation measure(s)
Main additional risk minimisation measures: • Communication to healthcare providers. • Review of rosuvastatin usage. • Restriction of samples. • Educational activities.

VI: 2.6 Planned post authorisation development plan

Table VI-8 List of studies in post authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
HYDRA (D3561C00004) A randomized, double-blind, placebo-controlled, multi-center, cross-over study	To assess efficacy of rosuvastatin 20 mg on LDL-C, compared to placebo, after 6 weeks of treatment in paediatric patients with HoFH To assess safety and tolerability of rosuvastatin in paediatric patients with HoFH	To see whether rosuvastatin is effective in treating children and adolescents with HoFH.	Planned	Q4 2015

HeFH Heterozygous familial hypercholesterolaemia; HoFH Homozygous familial hypercholesteroaemia; LDL-C Low density lipoprotein cholesterol; PK Pharmacokinetic; Q Quarter.

Studies which are a condition of the marketing authorisation

The above study is not a condition of the marketing authorisation.

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

Table VI-9 Major changes to the Risk Management Plan over time

Version	Date *(at time of authorisation)*	Safety concerns	Comment
2	Pending	CHARON study data added. Age range for paediatric indication broadened to include children 6 years of age and above	Clinical study report was finalized on 25 June 2013
3		Special patient populations removed as important risks and relevant information placed elsewhere within the RMP, as appropriate.	As an outcome of Procedure Nos. NL/H/0343-0346/001-004/058 and EMEA/H/A-29 Paed/1378.
		DDIs with clopidogrel and fusidic acid added as important identified interaction	As an outcome of Procedure No. NL/H/0343-0346/001-004/II/059.

DDI Drug drug interaction; RMP Risk management plan