VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Hypercholesterolaemia (high levels of cholesterol in the blood)

Raised cholesterol causes a disease called atherosclerosis (build up of fatty deposits in the arteries) and increases the risks of heart disease and stroke (loss of brain function). Globally, a third of of ischaemic heart disease (reduced blood supply to the heart) is attributable to high cholesterol. Overall, raised cholesterol is estimated to cause 2.6 million deaths (4.5% of total) and 29.7 million disability problems. Raised total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for cardiac circulatory disease and stroke. 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; the same serum cholesterol reduction for men aged 70 years can result in an average 20% reduction in heart disease occurrence in the next 5 years.
In 2008 the global prevalence (total number of people who have the disease over a period) of raised total cholesterol among adults (≥ 5.0 mmol/l) was 39% (37% for males and 40% for females). The prevalence of elevated total cholesterol in the WHO Region of Europe was 54% for both sexes.

Cardiovascular Events

The prevalence of the disorder varies depending on how abnormal lipid levels are defined and on the population studied. In patients with cardiac artery disease, the prevalence of abnormal lipid levels is as high as 80% to 88%, compared with approximately 40% to 48% in people of the same age without cardiac artery disease.

There is a strong correlation between body mass index (BMI) and incidence of hypercholesterolemia. The incidence is therefore higher in industrialized countries compared with developing countries. A worrisome development is the increase in the rate of risk factors, in developing countries, for cardiac artery disease (including raised cholesterol), while the risk factors for cardiac artery disease decrease in prevalence in industrialized countries. However, while there has been a steady decline in mortality from heart disease in the US since the early 1960s, it still remains the leading cause of death for both men and women of all races and ethnicities.

VI.2.2 Summary of treatment benefits

The efficacy of rosuvastatin in raised cholesterol control has been established in clinical studies, as well as in comparative studies with other drugs to control the cholesterol.

The results of one analyses of several studies supported the conclusion that rosuvastatin gave larger % reduction in cholesterol than twice the strength of atorvastatin (other drug to control the cholesterol) and that there was no significant difference between rosuvastatin and four times the atorvastatin strength.

The results of other analysis of studies, were consistent with the results that rosuvastatin gave significantly larger % reduction in cholresterol than twice the strength of simvastatin (other drug to control the cholesterol).

Thus, it can be concluded that among tested statins, rosuvastatin presented the most beneficial effects on the lipid profile in patients with hypercholesterolemia and exerts beneficial therapeutic effects in the management of a special type of familial (inherited) hypercholesterolaemia.

VI.2.3 Unknowns relating to treatment benefits

There is no available information on the use of the product in children below 6 years of age. The clinical trial experience in children and adolescent patients is limited and the long-term effects of rosuvastatin (>1 year) on puberty are unknown.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
- Severe muscular damage (Rhabdomyolysis)	In postmarketing experience, serious effects on skeletal muscle, as a kind of muscular necrosis called rhabdomyolysis, has been reported in patient treated rosuvastatin and other similar products. Reports of rhabdomyolysis with rosuvastatin are rare, but higher at the highest marketed dose (40 mg). Factors that may predispose patients to have muscle damage with the use of rosuvastatin and similar products include advanced age (≥65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy muscle damage increased at doses of rosuvastatin above the recommended dosage range. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies and, protease inhibitors, or cyclosporine and some other drugs.	•Rosuvastatin should be prescribed with caution in patients with predisposing factors for muscle damage, such as renal impairment, advanced age and hypothyroidism. •Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. •Rosuvastatin therapy should be discontinued if muscle damage is diagnosed or suspected. •Avoid concomitant treatment with other lipid-lowering therapies or other porducts wich could increase the risk of muscle damage. •Rosuvastatin therapy should be temporarily withheld in any patient with an acute, serious condition suggestive of muscle damage or predisposing to the development of renal failure secondary to it. •Early detection and monitoring.
- Effects on skeletal muscle and possible effects in blood and urine due to muscle damage (Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia, in the setting of rhabdomyolysis and myopathy)	In postmarketing experience, muscle damages have been reported in patients treated with rosuvastatin and other similar products. Factors that may predispose patients to have	•Rosuvastatin should be prescribed with caution in patients with predisposing factors for muscle damage, such as renal impairment, advanced age and hypothyroidism. •Patients should be advised to promptly

Risk	What is known	Preventability
	muscle damage with the use of rosuvastatin and similar products include advanced age (≥65 years), hypothyroidism, and renal insufficiency. The incidence of muscle damage increased at doses of rosuvastatin above the recommended dosage range. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies and some other drugs. Severe muscle damage could cause the development of renal failure secondary to it.	report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. •Rosuvastatin therapy should be discontinued if muscle damage is diagnosed or suspected. •Avoid concomitant treatment with other lipid-lowering therapies or other porducts wich could increase the risk of muscle damage. •Rosuvastatin therapy should be temporarily withheld in any patient with an acute, serious condition suggestive of muscle damage or predisposing to the development of renal failure secondary to it. •Early detection and monitoring.
-Hepatic effects (increased transaminases, hepatitis and jaundice)	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. Events as increased hepatic transaminases, jaundice and hepatitis have been reported. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. The reporting rate for serious hepatic events (consisting mainly of increased hepatic transaminases) in post-marketing use is	•Rosuvastatin should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal. •Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. •Early detection and monitoring.

Risk	What is known	Preventability
	higher at the 40 mg dose.	
- Inflammation of the pancreas (Pancreatitis)	Cases of pancreatitis (inflammation of the pancreas) have been reported in patient treated with rosuvastatin.	•Early detection and monitoring. •Patients should be advised to promptly report severe stomach pain
- Memory loss	Cases of memory loss have been reported in patient treated rosuvastatin.	•Early detection and monitoring.
- Increase in the amount of protein in the urine (Proteinuria)	Cases of increase in the amount of protein in the urine were detected in a small number of patients taking rosuvastatin and other similar drugs at their recommended doses during one clinical study. The increase in the amount of protein in the urine was more frequent in patients on rosuvastatin 40 mg. It was generally transient and not associated with worsening renal function.	•Although the clinical significance is unknown, dose reduction should be considered in patients on rosuvastatin 40 mg with unexplained persistent increase in the amount of protein in the urine.. •Early detection and monitoring.
-Diabetes mellitus	Some evidence suggests that some drugs to control the cholesterol could raise blood glucose and in some patients, and increase the risk of future diabetes. This risk, however, is outweighed by the reduction in vascular risk with the use of the treatment and therefore should not be a reason for stopping it. Patients at risk should be monitored both clinically and analytically.	•Early detection and monitoring.

Risk	What is known	Preventability
-Depression	Cases of depresion have been reported in patient treated rosuvastatin	•Early detection and monitoring.
-Sleep disorders (including insomnia and nightmares)	Cases of sleep disorders (including insomnia and nightmares) have been reported in patient treated rosuvastatin.	•Early detection and monitoring.
-Immune muscular damage (Immune-mediated necrotising myopathy)	Very rare cases of a kind of immune muscular damage, called immune-mediated necrotising myopathy, have been reported in patient treated rosuvastatin.	•Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. •Early detection and monitoring.
-Decreased platelet count (Thrombocytopenia)	Cases of decreased platelet count have been reported in post-marketing pharmacovigilance data.	•Early detection and monitoring.
-Serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis)	Cases of serious blistering condition of the skin, mouth, eyes and genitals, called Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported in patient treated rosuvastatin.	•Early detection and monitoring.
-Tendon disorders	Cases tendon injury has been reported in patient treated rosuvastatin	•Early detection and monitoring.
-Damage to the nerves which can cause numbness, pain, and weakness (Peripheral neuropathy)	Nerve damage resulting in numbness, pain and weakness has been reported with rosuvastatin (frequency unknown).	•Early detection and monitoring.
- Interactions with other drugs (Ciclosporin, various protease inhibitor combinations with ritonavir, clopidrogrel, gemfibrozil, eltrombopag, dronedarone,	The risk of muscle damage is increased when rosuvastatin is administered together with certain medicinal products as ciclosporin	•Avoid concomitant use with ciclosporin. •Whenever possible, alternative medications should be considered, and, if necessary,

Risk	What is known	Preventability
warfarin, other vitamin K antagonists, fusidic acid, ezetimibe and simeprevir)	(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), an oral contraceptive (the pill), hormone replacement therapy or ritonavir with lopinavir and/or atazanavir (used to treat the HIV infection). Muscle related events have been reported in post-marketing experience with rosuvastatin and fusidic acid given concurrently. Concomitant use with ciclosporin is contraindicated.	consider rosuvastatin dosing adjustments or temporarily discontinuing rosuvastatin therapy. •Early detection and monitoring.

Potential Risk

Risk	What is known
- Renal failure (including acute and chronic renal failure) and renal impairment	Rosuvastatin should not be used in any patient with an acute, serious condition suggestive of muscular damage or predisposing to the development of renal failure secondary to muscle damage. Rare cases of severe muscle damage, which were occasionally associated with impairment of renal function, have been reported with rosuvastatin, with all doses and in particular with doses> 20 mg. The 40 mg dose is contraindicated in patients with moderate renal impairment. Rosuvastatin is contraindicated in severe renal impairment.

Risk	What is known
- Liver failure (including necrosis of liver tissue and hepatitis)	A dose-related increase in liver enzymes has been observed in a small number of patients taking rosuvastatin; the majority of cases were mild and transient. Rosuvastatin must not be given in patients with active liver disease including unexplained, persistent elevations of liver enzymes. Rosuvastatin should be used with caution in patients who consume excessive quantities of alcohol and/or have a history of liver disease. It is recommended that liver function tests be carried out prior to, and 3 months following, the initiation of treatment. Rosuvastatin should be discontinued or the dose reduced if the level of liver enzymes is greater than 3 times the upper limit of normal. The reporting rate for serious liver events is higher at the 40 mg dose. Very rarely, hepatitis has been reported during treatment with rosuvastatin.
- Drug interactions with medications in lowering blood triglyceride levels (Drug-drug interactions with fibrates other than gemfibrozil)	Very rare cases of severe muscular damage have been reported with the use of other fibrates, used for control the cholesterol, in combination with other kind products to control the high level of cholesterol belonging to the same group of rosuvastatin.
- Lung problems (Interstitial lung disease)	Exceptional cases of lung problems have been reported with some drug belonging to the same group than Rosuvastatin, especially with long term therapy.
-Amyotrophic lateral sclerosis (ALS)	Amyotrophic lateral sclerosis is a neuron (nerve cells) disease caused by gradual deterioration and death of motor neurons (neurons responsible for voluntary movements). Symptoms of ALS include muscle weakness or stiffness during initial phase, which may degenerate in loss of the ability to speak, eat, move, and even breathe. Use of statins has been associated with an amyotrophic lateral sclerosis-like syndrome, however there is insufficient data to conclude on a causal relationship.

Missing information

Risk	What is known
- Children < 6 years of age	Rosuvastatin should not be given to children younger than 6 years, since the safety and efficacy of use in children younger than 6 years has not been studied.
-Studies in children with the aim to investigate possible interactions with other drugs	Interaction studies have only been performed in adults. The extent of interactions in children is not known.

VI.2.5 Summary of risk minimization 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 minimizing 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 minimization measures.

The MAH believes that the current contraindications, warnings and precautions within the SmPC and PL for ROSUVASTATIN 5 mg, 10mg, 20 mg and 40 mg film-coated tablets adequately inform health care professionals and patients about the benefit-risk of Rosuvastatin.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

N/A

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

Version	Date	Safety Concerns	Comment
2.0	December 2014	Identified Risks Potential Risks Missing information	Update of the summary table of risks to be aligned with that for the reference product Crestor, updated latest under procedure NL/H/0343-0346/IB/058/G:
3.0	22 September 2017	Important identified risks: •Rhabdomyolysis •Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy) •Increased	Update of the summary table of safety concerns to be aligned with that for the reference product

Version	Date	Safety Concerns	Comment
		transaminases, hepatitis, jaundice •Pancreatitis •Memory loss •Proteinuria •Diabetes mellitus •Depression •Sleep disorders (including insomnia and nightmares) •Immune Mediated Necrotising Myopathy (IMNM) •Thrombocytopenia / decreased platelet count •SJS / TEN (Stevens-Johnson syndrome and toxic epidermal necrolysis) •Tendon disorders •Peripheral neuropathy •Drug-drug interactions including ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, fusidic acid, ezetimibe and simeprevir Important potential risks: •Renal failure (including acute and chronic renal	

Version	Date	Safety Concerns	Comment
		failure) and renal impairment •Hepatic failure (including hepatic necrosis and fulminant hepatitis) •Interstitial lung disease (ILD) •Amytrophic lateral sclerosis (ALS) •Drug-drug interactions with fibrates (other than gemfibrozil) Missing information: •Children < 6 years of age •Drug-drug interaction studies in the paediatric population	