## VI.2 Elements for a public summary

### *VI.2.1 Overview of disease epidemiology*

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL, "bad cholesterol"), in the blood and early cardiovascular disease. Patients who have one abnormal copy (are heterozygous) of the low-density lipoprotein receptor (LDLR) gene may have premature cardiovascular disease at the age of 30 to 40 years. Having two abnormal copies (being homozygous) may cause severe cardiovascular disease in childhood. Heterozygous FH is a common genetic disorder, inherited in an autosomal dominant pattern, occurring in 1:500 people in most countries; homozygous FH is much rarer, occurring in 1 in a million births.

Combined hyperlipidemia is characterised by increased LDL and triglyceride concentrations, often accompanied by decreased high-density lipoprotein (HDL, “good” cholesterol). It is the most common inherited lipid disorder, occurring in approximately one in two hundred persons.

### *VI.2.2 Summary of treatment benefits*

Rosuvastatin is a medicine for improving blood fat levels and is used together with a low fat diet and exercise with the aim of reducing patients’ levels of triglycerides (a type of fat) and increasing their levels of ‘good’ cholesterol (HDL cholesterol). Rosuvastatin is to be used in adults at high risk of heart disease whose levels of ‘bad’ cholesterol (LDL cholesterol) are high. Rosuvastatin is effective in adults with high blood fat levels, with and without hypertriglyceridaemia (increased type of fat), regardless of race, sex, or age and in special populations such as diabetics, or patients with inherited blood fat increase.

### *VI.2.3 Unknowns relating to treatment benefits*

From the data, rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia (blood fat increase). In about 80 % of patients treated with 10 mg per day reached the levels of “bad” cholesterol (LDL-C) were reduced to the desirable values. The safety and efficacy of use in children younger than 6 years has not been studied.

### *VI.2.4 Summary of safety concerns*

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Abnormal muscle breakdown which can lead to kidney problems (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 rhabdomyolysis. | Rosuvastatin should be stopped and medical help should be sought immediately if any unusual aches or pains in muscles last longer than expected. |
| Muscle weakness, aches and pain, creatine kinase elevation, presence of myoglobin in blood and urine | 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 rhabdomyolysis. | Rosuvastatin should be stopped and medical help should be sought immediately if any unusual aches or pains in muscles last longer than expected. |
| Elevated liver enzymes, inflammation of the liver (hepatitis), jaundice | Increase in liver enzymes in the blood has been observed in 1 to 10 users in 10,000. Jaundice (yellowing of the skin and white of the eyes) and hepatitis (an inflamed liver) has been observed in less than 1 user in 10,000. | Carrying out this blood test (liver function test) before and during treatment with rosuvastatin. |
| Inflammation of the pancreas | Severe stomach pain (caused by inflamed pancreas) has been observed in 1 to 10 users in 10,000 | Risk is stated in the labelling. |
| Memory loss | Memory loss has been observed in less than 1 user in 10,000 | Risk is stated in the labelling. |

| Risk | What is known | Preventability |
|---|---|---|
| Increased amount of protein in the urine | An increased amount of protein in the urine has been reported in patients treated with rosuvastatin. In most cases, amount of protein in urine decreases or disappears spontaneously on continued therapy. | An assessment of kidney function should be considered during routine follow-up of patients treated with a dose of 30 or 40 mg. |
| Diabetes | There is an increased risk of developing diabetes while taking rosuvastatin. If you have high levels of sugars and fats in your blood, if you are overweight and if you have high blood pressure it is more likely that you will develop diabetes. | Patients at risk should be monitored according to national guidelines. |
| Depression | Depression has been observed; frequency is not known. | Risk is stated in the labelling. |
| Sleep disturbances | Sleep disturbances including sleeplessness and nightmares has been observed; frequency is not known. | Risk is stated in the labelling. |
| Muscle damage (Immune-mediated necrotising myopathy) | Muscle damage has been observed with rosuvastatin use. | Rosuvastatin should be stopped and medical help should be sought immediately if any unusual aches or pains in muscles last longer than expected. |
| Decreased platelet count | Signs of decreased number of blood platelets (more bleeding, easily than normal) have been observed in 1 to 10 users in 10,000. | Risk is stated in the labelling. |
| Stevens-Johnson syndrome/ toxic epidermal necrolysis (serious blistering condition of the skin, mouth, eyes and genitals) | Stevens-Johnson syndrome has been observed; frequency is not known. | Risk is stated in the labelling |
| Tendon injury | Tendon injury has been reported as a side effect of some statins. | Risk is stated in the labelling. |
| Disorder of the nerves (peripheral neuropathy) | Damage to the nerves of your legs and arms (such as numbness) has been observed in less than 1 user in 10,000. | Risk is stated in the labelling. |

| Risk | What is known | Preventability |
|---|---|---|
| Drug interaction including ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, ezetimibe, fusidic acid, and simeprevir. | Bleeding time may be prolonged if rosuvastatin is used together with warfarin or any other drug used for thinning the blood.<br>There is an increased risk of muscle weakness or pain when rosuvastatin is used together with drugs that increase its level in the blood. | Do not take rosuvastatin if you take a medicine containing a substance called ciclosporin (used, for example, after organ transplants).<br>Do not take rosuvastatin 30 or 40 mg tablets if you take other medicines called fibrates to lower your cholesterol.<br>Do not take rosuvastatin while taking fusidic acid or within 7 days after you have taken fusidic acid.<br>Dose adjustment may be necessary if rosuvastatin is used with other drugs that affect the rosuvastatin blood level. |

**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Loss of kidney function<br>(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 increased amount of protein in the urine and loss of kidney function. |
| Deterioration in liver function including injury of hepatic tissue (Hepatic failure: including hepatic necrosis and fulminant hepatitis) | Patients treated with rosuvastatin may be at an increased risk of developing this safety concern. Cases of increased hepatic transaminases, jaundice (yellowing of the skin and eyes) and hepatits (an inflamed liver) have been reported with rosuvastatin. |
| Progressive, fatal, neurodegenerative motor neuron disease (Amyotrophic Lateral Sclerosis) | Patients treated with rosuvastatin may be at an increased risk of developing this safety concern. |
| Lung disease (Interstitial lung disease) | Exceptional cases of interstitial lung disease have been reported with some statins (other blood fat lowering drugs of the same class), especially with long term use. Signs and symptoms may include shortness of breath, non-productive cough and deterioration in general health (weakness, weight loss and fever). If it is suspected that a patient has developed interstitial lung disease, statin therapy should be discontinued. |
| Interactions with medicines called fibrates (other than gemfibrozil) (Drug interactions: fibrates (other than gemfibrozil) | Patients should not take rosuvastatin 40 mg film-coated tablets (the highest dose) if they take other medicines called fibrates to lower their cholesterol.<br>Patients should talk to their doctor or pharmacist before taking rosuvastatin film-coated tablets if they take other medicines called fibrates to lower their cholesterol. They are advised to read package leaflet carefully, even if they have taken other medicines for high cholesterol before. |

**Missing information**

| Risk | What is known |
|---|---|
| Use in children under 6 years of age | Rosuvastatin should not be given to children younger than 6 years as there is no experience in the treatment of this patient group. |
| DDI studies in the paediatric population | There is no data on interactions with other medicinal products in the paediatric population. Studies have only been performed in adults. |

### *VI.2.5 Summary of risk minimisation measures by safety concern*

No additional risk minimisation measures are proposed.

### *VI.2.6 Planned post authorisation development plan*

Not applicable.

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

**Table 2.** Major changes to the Risk Management Plan over time

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| 1.0 | 23 January 2013 | Identified Risks: None<br>Potential Risks: None<br>Missing information: None | Not applicable. |
| 1.1 | 15 October 2013 | Identified Risks:<br>USE IN SPECIAL POPULATIONS (Use during pregnancy and lactation; Use in paediatric subjects; Use in elderly subjects; Use in subjects with severe hepatic impairment; Use in subjects with severe renal impairment; Use in Asian populations: increased plasma exposure)<br>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS including: Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy), tendon disorders and immune-mediated necrotising myopathy<br>Drug-drug interaction (including ciclosporin, various protease inhibitor combinations with ritonavir, fibrates, niacin, eltrombopag, dronedarone, ezetimibe, warfarin and other vitamin K antagonists)<br>Proteinuria<br>Diabetes mellitus | Risks added after request of the authority. |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | Potential Risks:<br>Interstitial lung disease<br>Missing information:<br>Long term use in children and adolescents;<br>Drug-drug interaction in children and adolescents | |
| 1.2 | 31 January 2014 | Identified Risks:<br>Rhabdomyolysis; Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy); Increased transaminases, hepatitis, jaundice; Pancreatitis; Memory loss; Proteinuria; Diabetes mellitus; Depression; Sleep disorders (including insomnia and nightmares); Immune-mediated necrotising myopathy; Thrombocytopenia/ decreased platelet count; Stevens-Johnson syndrome/toxic epidermal necrolysis; Tendon disorders; Peripheral neuropathy; Use in patients with severe hepatic impairment; Use in elderly patients; Use in paediatric patients; Use in patients with severe renal impairment; Use in pregnant or lactating women; Use in Asian populations: increased plasma exposure; Use in patients with genetic polymorphisms: increased plasma exposure; Drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists and ezetimibe.<br>Potential Risks:<br>Renal failure (including acute and chronic renal failure) and renal impairment; Interstitial lung disease; Use in patients to achieve very low LDL-C levels; Drug-drug interactions with fibrates (other than gemfibrozil)<br>Missing information:<br>Use in children under 6 years | Risks updated according to the originator. |
| 2.0 | 07 November 2014 | Important identified risks<br>Drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, warfarin, other vitamin K antagonists, ezetimibe and fusidic acid.<br>Missing information<br>Use in children under 6 years | Fusidic acid added to the list of drug interactions after request from authority<br>Risk updated according to the newly approved indication for rosuvastatin to be used in children older than 6 years |
| 2.1 | 22 October | There have been no changes in the safety concerns | The RMP was updated |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | 2015 | since version 2.0 of the RMP. | to be aligned with the changes in the SPC and PIL |
| 2.2 | November 2015 | There have been no changes in the safety concerns since version 2.0 of the RMP. | The RMP was updated to be aligned with the changes in the SPC and PIL |
| 3.0 | May 2016 | The following important identified risks have been deleted:<br>• Use in patients with severe hepatic impairment<br>• Use in elderly patients<br>• Use in paediatric patients<br>• Use in patients with severe renal impairment<br>• Use in pregnant or lactating women<br>• Use in Asian populations: increased plasma exposure<br>• Use in patients with genetic polymorphisms: increased plasma exposure<br><br>The following important potential risks have been deleted:<br>• Use in patients to achieve very low LDL-C levels<br>• Drug-drug interactions with fibrates (other than gemfibrozil)<br>The following important potential risks have been added:<br>• Hepatic failure: including hepatic necrosis and fulminant hepatitis<br>• Amyotrophic Lateral Sclerosis<br>The following risk has been added to 'Missing information':<br>• DDI studies in the paediatric population | The list of safety concerns was aligned with the reference product's list of safety concerns. |
| 3.1 | Aug 2016 | Drug interaction with simeprevir was added to the important identified risk:<br>• "Drug interactions: ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, warfarin and other vitamin K antagonists, ezetimibe, and, fusidic acid, and simeprevir"<br>The following important potential risk has been added:<br>• Drug interactions: Fibrates (other than gemfibrozil) | List of safety concerns was modified according to CMS comments (HU). RMS (DK) endorsed the HU proposal to include two safety concerns. |