

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hypercholesterolemia is characterized as condition with abnormally high levels of cholesterol in the blood. Heterozygous and homozygous familial hypercholesterolaemia (FH) is an inherited condition caused by an alteration in a gene, which results in a high cholesterol concentration in the blood.

Globally, a third of ischaemic heart disease 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 adjusted life years (DALYS), or 2.0% of total DALYS. Raised total cholesterol is a major cause of disease burden in both the developed and developing world as a risk factor for ischemic heart disease and stroke. In 2008 the global prevalence of raised total cholesterol among adults (≥ 5.0 mmol/l) was 39% (37% for males and 40% for females).

Heterozygous FH affects 1 in 500 of the UK population (around 108,000 people in England and Wales) and is the most common cause of markedly elevated cholesterol levels in children. Elevated serum cholesterol concentrations can lead to a greater than 50% risk of coronary heart disease (CHD) by the age of 50 years in men and at least 30% in women by the age of 60 years.

Homozygous FH is rarer with an incidence of approximately 1 case per one million. Symptoms appear in childhood, and are associated with early death from CHD.

VI.2.2 Summary of treatment benefits

Rosuvastatin Mylan belongs to a group of medicines called statins and is prescribed for high cholesterol level. This means patient is at risk from a heart attack or stroke.

Why it is important to keep taking Rosuvastatin Mylan:

- Rosuvastatin Mylan is used to correct the levels of fatty substances in the blood called lipids, the most common of which is cholesterol.
- There are different types of cholesterol found in the blood - 'bad' cholesterol (LDL-C) and 'good' cholesterol (HDL-C).
- Rosuvastatin Mylan can reduce the 'bad' cholesterol and increase the 'good' cholesterol.
- It works by helping to block body's production of 'bad' cholesterol. It also improves body's ability to remove it from blood.
- If high cholesterol is left untreated, fatty deposits can build up in the walls of blood vessels causing them to narrow.
- Sometimes, these narrowed blood vessels can get blocked which can cut off the blood supply to the heart or brain leading to a heart attack or a stroke. By lowering your cholesterol levels, you can reduce your risk of having a heart attack, a stroke or related health problems.
- Keep taking Rosuvastatin Mylan, even if it has got cholesterol to the right level, because it prevents cholesterol levels from creeping up again and causing build-up of fatty deposits. However, should stop if doctor tells to do so, or the patient has become pregnant.

Rosuvastatin is effective in adults with hypercholesterolaemia, with and without hypertriglyceridaemia, regardless of race, sex, or age and in special populations such as diabetics, or patients with familial hypercholesterolaemia.

Rosuvastatin has been shown to be effective at treating the majority of patients with type IIa and IIb hypercholesterolaemia, in studies including 435 patients with heterozygous FH, on 42 patients with homozygous FH. Another study including 917,802 men and women showed the adverse effects of rosuvastatin on the occurrence of major atherosclerotic cardiovascular disease events.

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.2.3 Unknowns relating to treatment benefits

There is limited experience with rosuvastatin use in children.

VI.2.4 Summary of safety concerns

Table 13 Part VI - Summary table of safety concerns

Important identified risks

Risk	What is known	Preventability
Unusual aches or pains in muscles / unpleasant muscle effects (Rhabdomyolysis)	Rosuvastatin is not to be taken if the patient has repeated or unexplained muscle aches or pains.	Patients are advised to talk to their doctors or pharmacist if they have a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines or have a muscle weakness that is constant.
Muscle aches and pains (Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in the setting of rhabdomyolysis and myopathy))	Rosuvastatin is not to be taken if the patient has repeated or unexplained muscle aches or pains. The doctor may decide to give the lowest dose (5 mg) if the patient is at risk of muscle aches and pains.	Patients are advised to talk to their doctors or pharmacist if they have a personal or family history of muscle problems, or a previous history of muscle problems when taking other cholesterol-lowering medicines or have a muscle weakness that is constant.
Increased levels of liver enzymes in the blood / an inflamed liver / yellowing of the skin and eyes (Increased transaminases, hepatitis, jaundice)	Rosuvastatin is not to be taken if the patient has liver disease. It is known to cause an increase in liver enzymes in the blood, an inflamed liver and yellowing of the skin and eyes as its side effects.	Patients are advised to talk to their doctor or pharmacist before taking Rosuvastatin if they have problems with their liver. The doctor might carry out a blood test (liver function

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Risk	What is known	Preventability
		test) before and during the treatment with rosuvastatin.
A severe stomach pain (inflamed pancreas) (Pancreatitis)	Severe stomach pain is been reported in patients treated with rosuvastatin.	The prescriber can monitor for any early symptoms, alternatively the patient should notify their doctor if early symptoms may occur.
Memory loss	Memory loss is been reported in patients treated with rosuvastatin.	By monitoring early symptoms. The patient should consult the doctor if any change in their memory or forgetfulness occurs.
Increase in the amount of protein in the urine (Proteinuria)	An increase in the amount of protein in the urine is been reported in patients treated with rosuvastatin.	An increase in the amount of protein in the urine, usually returns to normal on its own without having to stop taking rosuvastatin, however the patient can consult their doctor to get it monitored.
Serious blistering condition of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome and Toxic epidermal necrolysis)	Stevens-Johnson syndrome (serious blistering condition of the skin, mouth, eyes and genitals is been reported in patients treated with rosuvastatin.	The patient should consult their doctor or pharmacist if they get this side effect or any blistering condition should also be discussed.
Diabetes mellitus	Diabetes is been reported in patients treated with rosuvastatin.	While the patient is on rosuvastatin, the doctor will monitor closely if the patient has diabetes or are at risk of developing diabetes. The patient is likely to be at risk of developing diabetes if they have high levels of sugars and fats in your blood, are

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Risk	What is known	Preventability
		overweight and have high blood pressure.
Depression	Depression is been reported in patients treated with rosuvastatin.	The patient should consult their doctor or pharmacist if they are getting depressed or experience low mood.
Sleep disturbances (Sleep disorders (including insomnia and nightmares))	Sleep disturbances, including insomnia and nightmares have been reported in patients treated with rosuvastatin.	The prescriber should be aware about this safety concern and instruct the patient to contact the doctor immediately if such symptoms occur.
Immune-mediated necrotising myopathy	Autoimmune myopathy is a disorder that usually affects the muscles without involving the nerves/nervous system and for which cause is not known. The condition results in muscle weakness, fatigue, malaise and worsening of muscles.	The patient should consult their doctor or pharmacist for medical advice if any such symptoms occur.
Reduction in the platelet count below the normal lower limit (Thrombocytopenia/decreased platelet count)	Thrombocytopenia is a lower than normal number of platelets in the blood. Rosuvastatin, causal association with thrombocytopenia is not known. Currently SmPC / PIL has no information available.	The patient should consult their doctor or pharmacist for medical advice.
Tendon disorders	Tendon disorders, sometimes complicated by breaking or tearing have been reported in patients with rosuvastatin.	The prescriber should be aware about this safety concern and instruct the patient to contact the doctor

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Risk	What is known	Preventability
		immediately if such symptoms occur.
Drug-drug interactions including, ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe.	Before taking rosuvastatin, the patient has to tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines, including ciclosporin, ritonavir, gemfibrozil, warfarin and ezetimibe. Similarly for eltrombopag, dronedarone, itraconazole and other vitamin K antagonists.	The patient should consult their doctor or pharmacist before taking rosuvastatin if they take the following medicines: ciclosporin, various protease inhibitor combinations with ritonavir, gemfibrozil, eltrombopag, dronedarone, itraconazole, warfarin, other vitamin K antagonists and ezetimibe. The effects of these medicines could be changed by rosuvastatin or they could change the effects of rosuvastatin.
Damage to one or more of peripheral nerves (Peripheral neuropathy)	Damage to the nerves of legs and arms (such as numbness) are mentioned as a very rare possible side effect of rosuvastatin.	Patients should be advised to seek medical advice if they experience any numbness, tingling or burning in the arms or legs.

Important potential risks

Risk	What is known
Kidney problems (Renal failure (including acute and chronic renal failure) and renal impairment)	The patient should not take rosuvastatin if they have severe kidney problems. In addition they should talk to their doctor or pharmacist before taking rosuvastatin if they have any problems with their kidneys. The doctor may decide to give the lowest dose (5mg) if the patient has moderate kidney problems.
Liver problems (Hepatic failure: including hepatic	The patient should not take rosuvastatin if they have liver disease. They should talk to their doctor or pharmacist before

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Risk	What is known
necrosis and fulminant hepatitis)	taking rosuvastatin if they have problems with their liver. Possible side effects of rosuvastatin with liver problems are, an increase in liver enzymes in the blood, yellowing of the skin and eyes and an inflamed liver.
Nervous system disease that attacks nerve cells called neurons in brain and spinal cord (Amyotrophic lateral sclerosis)	Amyotrophic lateral sclerosis (ALS), is a nervous system disease that causes muscle weakness and impacts physical function. It is a type of motor neuron disease that causes nerve cells to gradually break down and die. ALS often begins with muscle twitching and weakness in an arm or leg, or sometimes with slurring of speech. Eventually, ALS can affect ability to control the muscles needed to move, speak, eat and breathe. ALS can't be cured and eventually leads to death. Rosuvastatin, causal association with ALS is not known. Currently SmPC / PIL has no information available. The patient should consult doctor or pharmacist if any of the early symptoms occur.
Interstitial lung disease describes a large group of disorders, most of which cause progressive scarring of lung tissue, eventually affecting ability to breathe and get enough oxygen into bloodstream (Interstitial lung disease)	Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease (DPLD), refers to a group of lung diseases affecting the interstitium (the tissue and space around the air sacs of the lungs). The scarring associated with interstitial lung disease eventually affects your ability to breathe and get enough oxygen into your bloodstream. Rosuvastatin may cause breathing problems, including persistent cough and/or shortness of breath or fever. However association of rosuvastatin with interstitial lung disease is unknown. Currently SmPC / PIL has no information available. The patient should contact doctor or pharmacist for advice if any of the symptoms occur.
Drug-drug interaction with fibrates (other than gemfibrozil)	The patient should not take rosuvastatin if they take other medicines called fibrates to lower your cholesterol. The patient should talk to their doctor or pharmacist if they take other medicines (fibrates) to lower cholesterol, even if other medicines were taken for high cholesterol before.

Missing information

Risk	What is known
Paediatric subjects	There is currently very little known to the Company with regards to the risk of taking rosuvastatin in paediatric patients. Since this RMP is for a generic product, the Company has not conducted any clinical trials and hence has no data available regarding this risk. However the PIL warns against taking rosuvastatin if the patient is under 10 years old and If the patient is below 18 years of age. Rosuvastatin 40 mg tablet is not suitable for use in children and adolescents below 18 years of age. In order to evaluate and assess this information, the Company proposes to closely monitor and assess the change in the benefit risk ratio of the product.

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. 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

This being a generic drug application, no post authorisation development has been planned.

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

The RMP for generic Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg Film-coated tablets application is updated from version 2 to version 3 in line with comments in Preliminary Renewal Assessment Report for Rosuvastatin 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets, SK/H /0133/001-003/II/005 by Mylan, dated 2-Mar-2016.