Summary of the Risk Management Plan for Masarov (Rosuvastatin calcium/Acetylsalicylic acid)

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Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for RA/LAN (Rosuvastatin calcium/acetylsalicylic acid). The RMP details important risks of RA/LAN, how these risks can be minimised, and how more information will be obtained about RA/LAN

's risks and uncertainties (missing information).

RA/LAN‘s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how RA/LAN should be used.

I. The medicine and what it is used for

RA/LAN is indicated for:

secondary prevention of cardiovascular events, as substitution therapy for adult patients who are adequately controlled therapy with the components administered concomitantly at equivalent therapeutic doses.

Posology

The recommended dose of Rosuvastatin calcium/ Acetylsalicylic acid 5 mg/100 mg, 10 mg/100 mg, 20 mg/100 mg, hard capsules is one capsule per day.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of RA/LAN together with measures to minimise such risks and the proposed studies for learning more about RA/LAN 's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of RA/LAN is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of RA/LAN are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RA/LAN. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	– Hypersensitivity reactions – Diabetes mellitus – Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in setting of rhabdomyolysis and myopathy) – Use in pregnancy and breastfeeding – Reye's syndrome – Haemorrhage (including gastrointestinal haemorrhage, increased menstrual bleeding during menorrhagia, Gastric or duodenal ulcer) – Liver impairment (Hepatic failure, including hepatic necrosis and fulminant hepatitis)

List of important risks and missing information	
Important potential risks	- NONE
Missing information	– Children and adolescents below 18 years of age

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Hypersensitivity reactions	
Evidence for linking the risk to the medicine	The purpose of the article is reported a case of DRESS syndrome in a patient with rosuvastatin use. As the onset of fever and rash correlated with recent travel to Europe, infectious etiology was assumed obscuring the correct diagnosis and this initial diagnostic approach. Malignancy and vasculitis became prominent differentials with the emerging evidence of multi-organ dysfunction (liver and kidneys), clinical deterioration, and generalized lymphadenopathy on computer tomography imaging; however, increased eosinophil count and elevated IgE levels were more consistent with DRESS syndrome. The onset of symptoms in DRESS is usually delayed, ranging from two to six weeks after initiation of the drug [7]. This patient reported that he was prescribed rosuvastatin a few years ago by his primary physician, but he never took it consistently. He was non-compliant with his rosuvastatin for about one year before starting it again about six weeks before the presentation. One possible explanation could be that inconsistent use of the drug causes initial sensitization and re-exposure causes a severe reaction manifesting as DRESS. It has been shown that following re-exposure, the symptoms may occur more rapidly and maybe more severe

Risk factors and risk groups	In general, allergic reactions to HMG-CoA reductase inhibitors appear to be rare, estimated to be 0.1%.[7] Despite the low frequency, the widespread use of these drugs has prompted reports of a wide variety of hypersensitivity reactions. These include rash, pruritus, eosinophilia, Stevens-Johnson syndrome, systemic lupus erythematosus - like syndrome, urticaria, and hypersensitivity pneumonitis Based on the manufacturers' labeling, the prevalence of skin rash with statins ranges from 0.8% to 4% (a causal relationship is generally not established in these cases). Generalized eczematous reactions were reported which were attributed to dysfunction of the skin barrier rather than an immunologic phenomenon. [8]
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.3, 4.4 PIL section Contraindications, Undesirable effects No risk minimisation measure

Diabetes mellitus	
Evidence for linking the risk to the medicine	

	Increased incidence of diabetes in persons taking rosuvastatin was reported in this trial, which included 17,802 men and women (average age 66 years) who were randomized into two groups: rosuvastatin (20 mg/day) or an inactive placebo drug. This trial was stopped early at 1.9 years when an interim analysis found a 44% lower incidence of adverse vascular events in the rosuvastatin group. There was a 26% higher incidence of diabetes in the rosuvastatin group. The results of JUPITER started a wave of discussion regarding potential risks and benefits of statin therapy.
Risk factors and risk groups	Recently, in a post-hoc analysis of the JUPITER trial, Ridker et al., concluded that participants with one or more major diabetes risk factor were at higher risk of developing diabetes than were those without a major risk factor; and benefits of statin therapy exceeded the diabetes hazard even in participants at high risk of developing diabetes.[9] Most recently, in a meta-analysis of 17 randomized controlled trials, rosuvastatin (20 mg/day), atorvastatin (80 mg/day) and pravastatin (40 mg/day) were found to increase risk of new onset diabetes (NOD) by 25%, 15% and 7%, respectively.[10].
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.4 PIL section Contraindications, Undesirable effects No risk minimisation measure

Myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia (in setting of rhabdomyolysis and myopathy)	
Evidence for linking the risk to the medicine	A clinical diagnosis of myopathy is made when there is muscle pain or weakness accompanied by a creatine kinase (CK) level more than ten times the upper limit of normal. Rhabdomyolysis is a severe form of myopathy with muscle breakdown leading to myoglobinuria, which may result in renal failure and death.
Risk factors and risk groups	Use of rosuvastatin 2.5 to 20 mg once a week has been shown to decrease LDL cholesterol by 25% and be tolerated by up to 70% of statin-intolerant patients. Twice-weekly or alternate-day regimens of rosuvastatin or atorvastatin alone or in combination with ezetimibe have also been well tolerated in patients with statin-induced myalgia. One randomized trial has shown that use of extended release fluvastatin 80 mg daily in patients with statin intolerance may be effective in reducing myalgic symptoms. In case of elevated CK levels (> 5xLSN), the treatment should be stopped.
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.2,4.3,4.4,4.5.

	PIL section Contraindications, Undesirable effects No risk minimisation measure

Use in pregnancy and breastfeeding	
Evidence for linking the risk to the medicine	In the SmPC is reported that The safety of acetylsalicylic acid in human pregnancy has not been established. Inhibition of prostaglandin synthesis can adversely affect pregnancy and / or embryo-fetal development. Data from epidemiological studies suggest that there is an increased risk of spontaneous abortion and cardiac malformations and gastroschisis following the use of a prostaglandin synthesis inhibitor in early pregnancy. Previous experiences on the use of ASA in pregnant women at daily doses of 50 to 150 mg during the second and third trimesters show no evidence of tocolysis, increased bleeding tendency or premature closure of the arterial duct. In animal studies, reproductive toxicity was observed at high doses of acetylsalicylic acid.

Risk factors and risk groups	Safety in pregnant women has not been established and there is no apparent benefit to use during pregnancy. Because HMG-CoA reductase inhibitors (statins) decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, this drug may cause fetal harm during pregnancy.
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.3,4.6 PIL section Contraindications, Undesirable effects No risk minimisation measure

Reye's syndrome	
Evidence for linking the risk to the medicine	Reye syndrome is an extremely rare but severe and often fatal disease. Death occurs in about 30–40% of cases from brainstem dysfunction.

Risk factors and risk groups	Reye syndrome is a rare disorder that appears to affect males and females in relatively equal numbers. The disorder occurs almost exclusively in individuals younger than age 18 years. Most cases occur at about age 6, with most affected individuals ranging in age from approximately four to 12 years. However, there have been rare instances in which Reye syndrome has affected infants and young adults. Evidence suggests that children and adolescents in rural and suburban areas appear to be affected more frequently than those in urban areas.
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.3. PIL section Contraindications, Undesirable effects No risk minimisation measure

Haemorrhage (including gastrointestinal haemorrhage, increased menstrual bleeding during menorrhagia)	
Evidence for linking the risk to the medicine	Major risk factors for upper GI events associated with aspirin use include a history of peptic ulcer or bleeding ulcer,37–42 concomitant use of other NSAIDs or antithrombotics,38,40,43–46 and *H. pylori* infection.39,47–49 Other factors that may increase the risk of peptic ulcers are smoking, excessive alcohol consumption, drug use, and emotional stress. These factors are considered to be environmental, as they contribute to ulcer formation by increasing gastric acid secretion, ultimately resulting in a weakened mucosal barrier.1 A
Risk factors and risk groups	All antithrombotic agents increase bleeding; aspirin, in particular, significantly increases the risk of major bleeding by about 60%.26 LDA is associated with intracranial or major extracranial events27 as well as prolonged bleeding;24 however, some of the most common side effects from aspirin are related to the upper GI tract. These range from mild conditions, such as dyspepsia, to more severe side effects, such as PUD and severe GI bleeding.24 Chronic aspirin consumption is associated with lower GI bleeding in more than 50% of aspirin users, indicating that GI injury is not only limited

	to the upper GI tract.28 Overall, aspirin has emerged as one of the most prominent causes of peptic ulcer bleeding in developed countries over the last 2 decades,29 and is associated with a 2- to 4-fold increased risk of upper GI bleeding and ulcers.30
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.3. PIL section Contraindications, Undesirable effects No risk minimisation measure

Liver impairment (Hepatic failure, including hepatic necrosis and fulminant hepatitis)	
Evidence for linking the risk to the medicine	Liver toxicity is a well recognized adverse effect of treatment with statins[1]. However pre-marketing studies have suggested that rosuvastatin may have a lesser potential to cause liver toxicity as compared with other statins.

Risk factors and risk groups	The mild ALT elevations associated with rosuvastatin therapy are usually self-limited and do not require dose modification; rosuvastatin should be stopped if ALT levels rise above 10-fold the ULN, or persist in being above 5-fold elevated or are associated with symptoms. In the clinically apparent liver injury attributed to rosuvastatin, recovery is usually complete within 1 to 2 months. Recurrence of injury with rechallenge has been reported and should be avoided. Cases of chronic hepatitis, but no instances of acute liver failure or vanishing bile duct syndrome, attributable to rosuvastatin have been reported. In cases of autoimmune hepatitis-like injury, corticosteroids have been used when recovery does not occur promptly. If corticosteroids are used, the dose and duration of treatment should be kept to a minimum, and careful followed up after stopping is essential.
Risk minimisation measures	*Routine risk minimisation measures* The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.3. PIL section Contraindications, Undesirable effects No risk minimisation measure

Missing information

Children and adolescents below 18 years of age	
Evidence for linking the risk to the medicine	SmPC of medicinal product Rosuvastatin calcium/acetylsalicylic acid.
Risk factors and risk groups	The safety and efficacy of rosuvastatin/acetylsalicylic acid in children and adolescents under the age of 18 have not been established. Rosuvastatin/ acetylsalicylic acid is not recommended for use in patients under the age of 18.
Risk minimisation measures	Routine risk minimisation measures The safety information in the proposed product information is aligned to the reference medicinal product. SmPC section 4.4 PIL section Contraindications, Undesirable effects No risk minimisation measure

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation for RA/LAN.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for RA/LAN.