Summary of risk management plan for rosuvastatin/perindopril/indapamide

This is a summary of the risk management plan (RMP) for rosuvastatin/perindopril/indapamide. The RMP details important risks of rosuvastatin/perindopril/indapamide, how these risks can be minimised, and how more information will be obtained about rosuvastatin/perindopril/indapamide's risks and uncertainties (missing information).

Rosuvastatin/perindopril/indapamide 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how rosuvastatin/perindopril/indapamide should be used.

Important new concerns or changes to the current ones will be included in updates of rosuvastatin/perindopril/indapamide 's RMP.

I. The medicine and what it is used for

Rosuvastatin/perindopril/indapamide is authorised for substitution therapy in adult patients adequately controlled with rosuvastatin, perindopril and indapamide given concurrently at the same dose level as in the combination for treatment of essential hypertension and one of the following coincident conditions: primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb) or homozygous familial hypercholesterolaemia (see SmPC for the full indication). It contains rosuvastatin, perindopril and indapamide as the active substances and it is given by oral route.

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

Important risks of rosuvastatin/perindopril/indapamide, together with measures to minimise such risks and the proposed studies for learning more about rosuvastatin/perindopril/indapamide '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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of rosuvastatin/perindopril/indapamide 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 rosuvastatin/perindopril/indapamide. 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	Skeletal muscle effects: rhabdomyolysis, myopathy, myositis, myalgia, creatine kinase increases, myoglobinaemia, and myoglobinuria
	Dual blockade of renin-angiotensin-aldosterone system (RAAS)
	Renal impairment (including renal failure)
	Hepatic effects: permanently increased transaminases, hepatitis, jaundice, hepatic encephalopathia, hepatic impairment
	Hypersensitivity reactions (including angioedema, intestinal angioedema, concomitant use of mTOR inhibitor, photosensitivity and anaphylactoid reactions)
	Electrolyte abnormalities including hypo- and hyperkalaemia
	Neutropenia/agranulocytosis
	Stevens-Johnson syndrome and Toxic epidermal necrolysis
	Use during pregnancy and lactation
	Drug interactions: drug-drug interactions including: ciclosporin, various protease inhibitors with ritonavir, gemfibrozil, clopidogrel, eltrombopag, dronedarone, warfarin and other vitamin K antagonists, fusidic acid and ezetimibe.
Important potential risks	Interstitial lung disease
	Off label use
Missing information	Use in paediatric population
	Use in patients undergoing dialysis
	Use in patients with untreated decompensated heart failure
	Long-term safety of the combination

II.B Summary of important risks

The safety information in the proposed Product Information is aligned with the Product Information of reference monocomponents.

Important identified risk: **Skeletal muscle effects: rhabdomyolysis, myopathy, myositis, myalgia, creatine kinase increases, myoglobinaemia, and myoglobinuria** *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).*	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Older age (65 and older), high statin dosage, renal disease, female gender, interaction with other drugs. Concomitant treatment with drugs that can increase plasma levels of rosuvastatin and/ or increased frequency of muscoskeletal adverse events/reactions (including ciclosporin, various protease inhibitor combinations with ritonavir, clopidogrel, gemfibrozil, eltrombopag, dronedarone, fusidic acid, colchicine and ezetimibe).
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.2, 4.3, 4.4, 4.5, and section 4.8. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: ***Dual blockade of renin-angiotensin-aldosterone system (RAAS)*** Combining medicines that affect hormone system that regulates blood pressure	
Evidence for linking the risk to the medicine	Summary of Product's characteristics PRAC assessment report for renin-angiotensin system (RAS)-acting agents (EMEA/H/A-31/1370)
Risk factors and risk groups	Patients with diabetes mellitus Patients with diabetic nephropathy *Patients with renal impairment (GFR < 60 ml/min/1.73 m2)*
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.4, 4.5, and section 5.1. Other routine risk minimisation measures beyond the Product

	Information: Legal status: prescription only

Important identified risk: **Renal impairment (including renal failure)** Kidney problems	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Patients with the already existing renal impairment. The event is more common with post-myocardial infarction patients and/or patients with heart failure and the risk is increased if they are sodium-depleted or dehydrated secondary to excessive diuresis. Patients on the NSAID therapy. *Elderly.*
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.2, 4.3, 4.4, and section 5.2. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation in SmPC section 4.4 that the product should be stopped immediately if angioedema or other serious hypersensitivity occur. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Hepatic effects: permanently increased transaminases, hepatitis, jaundice, hepatic encephalopathia, hepatic impairment** Liver problems	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	*Patients with the already existing hepatic impairment.*
Risk minimisation measures	Routine risk communication:

	Information in SmPC section 4.2, 4.3, 4.4, and section 4.8, 5.2. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Hypersensitivity reactions (including angioedema, intestinal angioedema, concomitant use of mTOR inhibitor, photosensitivity and anaphylactoid reactions)** Allergic reactions incuding swelling of face, neck, lips and throat	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Heredity, gender, race and age; environmental factors like pollution, allergen levels, and dietary changes. The most important demographic factor modifying angioedema risk is race, with blacks having 4-fold higher risk of angioedema compared to non-blacks. Patients undergoing desensitisation treatment with hymenoptera venom, patients during low density lipoprotein apheresis and patients dialysed with high-flux membranes are also more prone to developing anaphylaction reaction.
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.3, 4.4, 4.5, and section 4.8. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: Electrolyte abnormalities including hypo- and hyperkalaemia Changes in kalium levels in the blood	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Renal disease, acute or chronic diarrhoea, vomiting, dehydration, heat exhaustion, certain medications (diuretics), very young age, old age.
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.4, 4.5, 4.6 and section 5.1.

	Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Neutropenia/agranulocytosis** Change in number of different blood cells	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Patients with the cancer (leukemia, lymphoma), aplastic anaemia or autoimmune diseases (lupus, rheumatoid arthritis) Patients who are exposed to certain toxic chemicals (pesticides, arsenic, benzene) Patients with genetic conditions (Wiskott-Aldrich syndrome, May-Hegglin syndrome).
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.4, and section 4.8. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Stevens-Johnson syndrome and Toxic epidermal necrolysis**	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Risk of developing SJS remains unidentifiable in most of the cases. - Drugs with long half-lives are more likely to cause such fatal reactions than those with short half-lives. - Viral infections. - Weakened immune system. - A history of Stevens-Johnson syndrome. - A family history of Stevens-Johnson syndrome. - Having a gene called HLA-B 1502. People have an increased risk of Stevens-Johnson syndrome, particularly if you take certain drugs for seizures or mental illness. Families of Chinese, Southeast Asian or Indian descent are

	more likely to carry this gene.
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation in SmPC section 4.4 that the product should be stopped immediately if angioedema or other serious hypersensitivity occur. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Use during pregnancy and lactation**	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Common teratogens include infections, drugs, and physical agents. Malformations are most likely to result if exposure occurs between the 2nd and 8th week after conception when organs are forming. Pregnant women exposed to teratogens are counselled about increased risks and referred for detailed ultrasound evaluation to detect malformations. Common infections that may be teratogenic include herpes simplex, viral hepatitis, rubella, varicella, syphilis, toxoplasmosis, and cytomegalovirus and coxsackievirus infections. Commonly used drugs that may be teratogenic include alcohol, tobacco, cocaine, and some prescription drugs.
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.3, 4.4 and section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important identified risk: **Drug interactions: drug-drug interactions including: ciclosporin, various protease inhibitors with ritonavir, gemfibrozil, clopidogrel, eltropomag, dronaderone, warfarin and other vitamin K antagonists, fusidic acid and ezetimibe** Interactions with various other drugs	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	- smoking - drinking alcohol - older people - people having poor health
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.2, 4.3, 4.4 and section 4.5. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important potential risk: **Interstitial lung disease** Lung disease	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	Not known. Among the numerous possible causes are most connective tissue disorders, occupational lung exposures and many drugs.
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.4 and section 4.8. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Important potential risk: **Off label use** Use of the approved medicine differs from the situation described in the Patient leaflet	
Evidence for linking the risk to the medicine	Summary of Product's characteristics Literature
Risk factors and risk groups	- many drugs in therapy - doctors under pressure
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.1 and section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Missing information: **Use in paediatric patients**	
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.2, 4.5, and sections 4.8, 5.2. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Missing information: **Use in patients undergoing dialysis**	
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.3, 4.4, and sections 4.8, 5.2. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Missing information: **Use in patients with untreated decompensated heart failure**	
Risk minimisation measures	Routine risk communication: Information in SmPC section 4.3.

	Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

Missing information: **Long-term safety of the combination**	
Risk minimisation measures	Routine risk communication: No risk minimisation activities in addition to prescription only are proposed. Should the PhV activities uncover additional data, another risk minimisation activities may be proposed if necessary. Other routine risk minimisation measures beyond the Product Information: Legal status: prescription only

II.C Post-authorisation development plan

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

Not applicable.

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

Not applicable.