Part VI: Summary of the risk management plan

Summary of risk management plan for Noradrenalin “Macure” (noradrenaline)

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

Noradrenalin Macure's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Noradrenalin Macure should be used.

I. The medicine and what it is used for

Noradrenalin “Macure” is authorised for peripheral shock (see SmPC for the full indication). It contains noradrenaline as the active substance and it is given by intravenous infusion

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

Important risks of Noradrenalin Macure, together with measures to minimise such risks and the proposed studies for learning more about Noradrenalin Macure'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 Noradrenalin Macure is not yet available, it is listed under ‘missing information’ below>.

II.A List of important risks and missing information

Important risks of Noradrenalin Macure are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Noradrenalin Macure. 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	Overdose
	Bradycardia and cardiac arrhythmias
	Hypertension
	Dyspnea
	Extravasation
	Necrosis and Peripheral ischaemia (including gangrene of the extremities)

List of important risks and missing information	
Important potential risks	Use during pregnancy
	Drug-drug interaction
Missing information	Use in patients with renal or hepatic insufficiency
	Use in paediatric population

II.B Summary of important risks

Important identified risk - Overdose	
Evidence for linking the risk to the medicine	DAP, on MHRA website and proprietary data from pharmacovigilance departments in Switzerland and USA.
Risk factors and risk groups	Elderly patients can be considered a risk group, mainly due to co-morbidities and preexisting medication.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.9 SmPC section 4.4 where advice is given on monitoring blood pressure, diuresis and ECG PL section 3

Important identified risk - Bradycardia and cardiac arrhythmias	
Evidence for linking the risk to the medicine	DAP, on MHRA website, proprietary data from pharmacovigilance departments in Switzerland and USA, and the SmPCs reference products.
Risk factors and risk groups	Elderly patients and concomitant cardiac disorders are risky situation in the administration of noradrenaline. Clinicians have the knowledge to use the suitable lower dose in case of acute hypotension induced by myocardial infarction. Patients with hypertrophic obstructive cardiomyopathy should not receive noradrenaline, or any catecholamine with a beta-1 effect for that matter. Particular caution should be observed in patients with coronary, mesenteric or peripheral vascular thrombosis because noradrenaline may increase the ischemia and extend the area of infarction. Similar caution should be observed in patients with hypotension following myocardial infarction and in patients with Prinzmetal's variant angina.
Risk minimisation measures	Routine risk minimisation measures

	SmPC sections 4.5, 4.6, 4.8, 4.9 and 5.3 SmPC section 4.4 where advice is given on monitoring ECG PL sections 2 and 4

Important identified risk - Hypertension	
Evidence for linking the risk to the medicine	DAP, on MHRA website, proprietary data from pharmacovigilance departments in Switzerland, and the SmPC reference products
Risk factors and risk groups	Elderly patients and patients with respiratory disease are in a risky situation. Clinicians have the knowledge to use suitable lower dose of noradrenaline in case of risk group patients as reported in preventability section
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4, 4.5, 4.8 and 4.9 SmPC section 4.4 where advice is given on monitoring the blood pressure and adjust plasma volume PL sections 2 and 4

Important identified risk - Dyspnoea	
Evidence for linking the risk to the medicine	DAP, on MHRA website, proprietary data from pharmacovigilance departments in Switzerland, and the SmPC reference products
Risk factors and risk groups	Elderly patients and patients with respiratory disease are in a risky situation. Clinicians have the knowledge to use suitable lower dose of noradrenaline in case of risk group patients as reported in preventability section.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8 PL section 2

Important identified risk - Extravasation	
Evidence for linking the risk to the medicine	MedScape Noradrenaline Extravasation Research, Updated: November, 2014
isk factors and risk groups	Risk factors for intravenous extravasation are presented in the following: o Small veins o Brittle veins (elderly patients) o Reduced physical health (cancer patients) o Sclerosizing veins o Rolling veins Poor circulation (if the needle is placed in an arm with edema) o Obstructed vena cava (raised venous pressure may cause leakage) o Conditions such as diabetes and radiation damage o Obesity
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 SmPC section 4.4 where advice is given on monitoring blood pressure and to adjust plasma volume. PL section 4

Important identified risk - Necrosis and Peripheral ischaemia (including gangrene of the extremities)	
Evidence for linking the risk to the medicine	MedScape Noradrenaline Peripheral ischaemia and Necrosis Research, Updated: October, 2014
Risk factors and risk groups	Risk factors for Peripheral ischaemia and Necrosis are presented in the following: o Intravenous extravasation o Small veins o Brittle veins (elderly patients) o Reduced physical health (cancer patients) o Sclerosizing veins o Rolling veins Poor circulation (if the needle is placed in an arm with edema) o Obstructed vena cava (raised venous pressure may cause leakage) o Conditions such as diabetes and radiation damage o Obesity
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8 and 5.1 SmPC section 4.4 where advice is given on monitoring blood pressure and to adjust plasma volume.

Important potential risk - Use during pregnancy	
Evidence for linking the risk to the medicine	DAP, on MHRA website, proprietary data from pharmacovigilance departments in Switzerland and USA, and the SmPCs reference products
Risk factors and risk groups	Pregnant women (late pregnancy) Fetus
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.6 and 5.3 PL section 2

Important potential risk -Drug-drug interaction	
Evidence for linking the risk to the medicine	DAP, on MHRA website, proprietary data from pharmacovigilance departments in Switzerland and USA, and the SmPCs reference products
Risk factors and risk groups	Patients taking other medicinal products
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5 PL section 2

Missing information - Use in patients with renal or hepatic insufficiency	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2

Missing information - Use in paediatric population	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2

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 of Noradrenalin Macure.

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

There are no studies required for Noradrenalin Macure.