VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Myocardial infarction

Myocardial infarction is one of the five main manifestations of coronary heart disease, namely stable angina pectoris, unstable angina pectoris, myocardial infarction, heart failure and sudden death. Myocardial infarction is defined by the demonstration of myocardial cell necrosis due to significant and sustained ischaemia. It is usually, but not always, an acute manifestation of atherosclerosis-related coronary heart disease. Myocardial infarction results from either coronary heart disease, which implies obstruction to blood flow due to plaques in the coronary arteries or, much less frequently, to other obstructing mechanisms (e.g. spasm of plaque-free arteries). The clinical presentation of Myocardial infarction varies from a minor coronary event to life-threatening clinical situations or sudden death. Those who survive the initial event are vulnerable to repeat attacks of Myocardial infarction. [2]
Coronary heart disease is a major cause of death and disability in developed countries. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years. Although many cases of myocardial infarction appear to occur without warning, there is a large reservoir of detectable advanced silent coronary heart disease from which these apparently sudden events evolve. Such patients frequently have an ominous coronary risk profile and signs of pre-symptomatic coronary heart disease. Approximately 2–4% of the general population has silent coronary ischemia which despite being an asymptomatic condition can be actually detected with an exercise test or ambulatory ECG monitoring. The prevalence of this condition might be considerable higher in men with two or more major coronary risk factors (10%), and especially in patients with known coronary heart disease, e.g., 25–50% in those with stable angina detected through exercise testing or ambulatory monitoring. [3]

Altogether, from the early to mid 1980s until the mid to late 1990s within the context of a decline in coronary disease mortality, the incidence of myocardial infarction declined little (even increased in certain groups) while case fatality improved. This suggests that medical care played a major role in the genesis of the decline of coronary deaths. [4]

Tachyarrhythmia

Ventricular tachyarrhythmias include potentially lethal episodes of sustained ventricular tachycardia and ventricular fibrillation as well as hemodynamically tolerated ventricular ectopic activity. Sustained Ventricular tachyarrhythmia or Ventricular fibrillations may develop in the setting of acute myocardial infarction or as clinical sequelae of advanced cardiomyopathy. Over the past few decades, there has been a gradual decline in the incidence of life-threatening ventricular tachyarrhythmias which has been largely driven by upstream treatments for and prevention of coronary artery disease and its sequelae. In addition primary prevention implantable cardioverter-defibrillators (ICDs) have improved survival in patients at risk for malignant ventricular arrhythmias and sudden cardiac death. [5]

VI.2.2 Summary of treatment benefits

In the recently published “Effect of Metoprolol in Cardioprotection during an Acute Myocardial Infarction” 270 patients with STEMI (certain type of myocardial infarction) (Killip Class 2 or less) were included in a trial. In this trial they receive within 6 h of onset of symptoms intravenous metoprolol or no metoprolol (randomly assigned). The infarct size was smaller after intravenous metoprolol compared with control (25.6 ± 15.3 gm vs

32.0 ± 22.2 gm, P = 0.012, measured by magnetic resonance imaging). This illustrates that a commonly used medication may play a significant role in cardioprotection in the setting of (…) STEMI.

The ideal duration of treatment with orally taken beta blockers after a STEMI: At present most patients are treated indefinitely with beta blockers after a STEMI. This is mostly based on evidence from a large meta-analysis that included 50.000 patients and showed a 23% reduction in mortality at a mean follow up of 1.4 years. [6]

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hypersensitivity (allergies) to Metoprolol, any of the excipients or other beta blocking agents	Patients might experience allergic reactions (such as allergic rhinitis, rash, cough, even anaphylactic shock) if they are hypersensitive to metoprolol, other beta blocking agents or any of the excipients. Metoprolol Carino 1 mg/ml solution for injection is indicated for emergency use, so that severe allergic reactions could seriously threaten the patient's life.	Patients with known hypersensitivity to metoprolol, any of the excipients or other beta blocking agents must not be treated with Metoprolol Carino 1 mg/ml solution for injection. Patients should always be closely monitored for changes of their vital signs.
Pathological or medicinal induced changes of the cardiac conduction, such as AV Block or therapy with anti-arrhythmic agents	Metoprolol acts by dampening the exciting impulses on the heart by certain neurotransmitters such as adrenalin, so that it slows the hearts rhythm amongst other things. In the case of changes to the electrical conduction either by diseases or drugs, this dampening might lead to a total block of the electrical conduction and thus induce cardiac arrest.	Patients with 2nd or 3rd degree AV block, sick sinus syndrome and sinoatrial block and patients who are treated with calcium antagonists such as verapamil and diltiazem or other anti-arrhythmic agents should not be treated with Metorpolol Carino 1 mg/ml solution for injection. Special care is necessary in patients with 1st degree AV block.
Heart failure	In overt heart failure, the heart is not any longer able	Patients with overt heart failure should not be

Risk	What is known	Preventability
	to maintain the necessary performance to sufficiently supply the rest of the body with oxygenated blood. As metoprolol depresses the heart and slows it rhythm down, this might worsen the symptoms of the underlying disease.	treated with Metoprolol Carino 1 mg/ml solution for injection.
Shock	Shock is known as a life-threatening medical condition of low blood perfusion to tissues resulting in cellular injury and inadequate tissue function due to various reasons. The lowering of blood pressure and heart rate by metoprolol could seriously exacerbate the disease mechanics and endanger the patient's life.	Metoprolol Carino 1 mg/ml solution for injection must not be used in patients with shock.
Bradycardia (low heart rate)	As mentioned above, metoprolol lowers the heart rate. In patients with a low heart rate before the administration of metoprolol, the resulting reduction of the heart rate might be so severe, that the body cannot compensate it with other mechanisms and circulation collapses.	Metoprolol Carino 1 mg/ml solution for injection must not be used in patients with bradycardia. Patients should always be closely monitored for any changes of their vital signs.
Hypotension (low blood pressure)	As mentioned above, metoprolol lowers the blood pressure. In patients with a low blood pressure before the administration of metoprolol, the resulting reduction of the blood pressure might be so severe, that the body cannot compensate it with other mechanisms and circulation collapses.	Metoprolol Carino 1 mg/ml solution for injection must not be used in patients with hypotension. Patients should always be closely monitored for any changes of their vital signs.
Acidosis	Acidosis is a process causing increased acidity in the blood and other body	Patients with acidosis should not be treated with

Risk	What is known	Preventability
	tissues (i.e. an increased hydrogen ion concentration). Patients with acidosis are more likely to develop severe cardiac events such as life threatening arrhythmia. Metoprolol could worsen acidosis by influence in different metabolic processes.	Metoprolol Carino 1 mg/ml solution for injection.
Bronchial hyperresponsiveness	Due to its pharmacological properties, metoprolol can lead to severe bronchial spasm in patients with bronchial hyperresponsiveness (e.g. bronchial asthma). As the indication is limited to emergency and hospital treatment, it has to be assumed, that the patient's overall condition is severely impaired, so that severe respiratory adverse events could be life threatening.	Patients with bronchial hyperresponsiveness should not be treated with Metoprolol Carino 1 mg/ml solution for injection. Patients should always be closely monitored for any changes of their vital signs.
Late stages of peripheral arterial disease (specific stage of impaired peripheral perfusion)	As stated above, metoprolol lowers the blood pressure and heart rate, which can lead to a reduction of peripheral perfusion. In patients with late stages of peripheral arterial disease, peripheral perfusion is already impaired, so that the additional reduction could induce tissue damage.	Metoprolol Carino 1 mg/ml solution for injection should not be used in patients with late stages of peripheral arterial disease. Patients should always be closely monitored for changes of their overall condition.
Concomitant administration of MAO inhibitors (specific kind of medication for e.g. depression)	Monoamine oxidase (MAO) is a certain type of protein, which metabolises certain neurotransmitters such as dopamine, which are amongst other things responsible for excitation on the heart. Due to feedback mechanisms metoprolol can induce an increase of these	Metoprolol Carino 1 mg/ml solution for injection should not be used in patients who are treated with MAO inhibitors.

Risk	What is known	Preventability
	neurotransmitters. If they cannot be metabolised because of treatment with MAO inhibitors, excessive hypertension could be induced.	

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Hypoglycemic states	Due to the pharmacological properties of metoprolol, metoprolol can induce hypoglycaemia (low blood sugar) and mask the symptoms of hypoglycaemia such as tremor and tachycardia. Severe states of hypoglycaemia can be life threatening, especially in patients with reduced general condition.
Paeochromocytoma	Phaeochromocytoma is a tumour of the adrenal glands which produces independently hormones such as norepinephrine. Metoprolol could induce excessive hypertension in the affected patients.
Hepatic impairment	Metoprolol is mainly metabolised in the liver. In case of severe hepatic impairment, metoprolol cannot be degraded fast enough, so that it accumulates in the patient's blood. Symptoms of overdose could result. Therefore, treating physicians should consider reducing the dose of metoprolol accordingly.
Psoriasis	Metoprolol might exacerbate psoriasis (autoimmune disease characterised by patches of abnormal skin) in patients with pre-existing psoriasis, but also lead to a development of psoriasis and psoriasis like rash. In patients who are predisposed for development of psoriasis (for example by family anamnesis), metoprolol should only be used after careful assessment of the risks and benefits.
Severe anaphylactic reactions	Metoprolol can aggravate the course of anaphylactic reactions, especially in patients undergoing desensitization therapy. Standard treatment of anaphylactic reactions is adrenalin, whose efficacy is reduced by beta blocking agents such as metoprolol, due to the fact, that they bind to the same receptors.
Patients with cardiovascular risk factors	Acute high-dose metoprolol is associated with low heart rate, low blood pressure and stroke in patients with cardiovascular risk factors undergoing non-cardiac surgery. Metoprolol should be avoided in these patients
Withdrawal of Metoprolol	The risk of coronary events, including sudden cardiac death, may be increased after withdrawal of the beta blocking agent due to certain types of rebound

Risk	What is known (Including reason why it is considered a potential risk)
	mechanisms. Therefore, therapy should be continued with oral beta blocking agents after the patient's rhythm disturbances are under control. These oral beta blocking agents should not be withdrawn suddenly.
Patients with acute myocardial infarction	Patients with acute myocardial infarction displayed an increased risk of cardiogenic shock under metoprolol therapy. As haemodynamically unstable patients are particularly affected, metoprolol must be given only after haemodynamic stabilisation of the infarction patient
False positive doping tests	Beta blocking agents are prohibited in particular sports, therefore metoprolol might lead to a positive doping test. Athletes should be informed accordingly.
Use during Pregnancy and lactation	Metoprolol reduces blood flow to the placenta and is therefore capable of causing foetal growth abnormalities. Miscarriages, premature delivery and intrauterine foetal death have been observed following administration of other beta blockers. There is also a risk of neonatal bradycardia, hypotension and hypoglycaemia. Metoprolol is excreted in breast milk in a concentrated form. During pregnancy (and particularly during the first three months), metoprolol should be used only following strict patient selection and assessment of the risks and benefits. Treatment with metoprolol should be discontinued 48 72 hours before the calculated delivery date. If this is not possible, careful clinical monitoring of neonates is required for 48 72 hours after delivery. Breast-fed infants should be monitored for symptoms of beta blockade. The amount of metoprolol ingested via breast milk can be reduced by stopping breast-feeding until 3 4 hours after administration of the medicinal product

Missing information

Risk	What is known
Use in children	The safety and efficacy of metoprolol in children has not been established.

VI.2.5Summary 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 (PL). 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

Not applicable.

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

Major changes to the Risk Management Plan over time

Version	**Date**	**Safety Concerns**	**Comment**
1.0	04.09.2017	Not applicable.	The initial RMP.