VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Landiolol is indicated for the short-term acute management or prevention of an irregular or fast heartbeat. In adults landiolol is used to treat a fast heart beat called sinus tachycardia (ST), or is used to treat a fast and irregular heart beat called supraventricular tachyarrhythmia (SVT). It is used during or after a surgery or in any other situation when slowing down the heartbeat is required.

ST and SVTs as a disease group comprise several types of cardiac arrhythmia. They occur commonly and are more prevalent in an aging population. While SVTs are known to occur spontaneously in patients with no history of heart disease, a number of factors have been identified that increase the risk of triggering arrhythmias. During and after a surgery, the risk of arrhythmias is up to 100-fold increased vs. the general population. Frequencies of occurrence range from 0.5% in the general population to ca. 50 - 60% in patients undergoing e.g. cardiac surgeries. Other known risk factors are e.g. advanced age, hypertension, diabetes, obesity, smoking, and cardiovascular disease. ST may also occur as symptoms of other diseases, e.g. infections, malignancies, cardiac diseases, shock.

VI.2.2 Summary of treatment benefits

Landiolol shows potent inhibiting activity on a specific receptor (beta1-receptor) which is mainly located in the heart and which is responsible for increasing the heart rate and the blood pressure.

Landiolol slows down the heart beat and is therefore used to treat fast heartbeat. Due to its rapid onset and very short duration of action, landiolol is used for the emergency management as well as during surgical procedures if a brief duration of action is requiring. Moreover, landiolol is used for the prevention of fast heartbeat.

The beneficial effects of landiolol have been demonstrated in a large number of clinical trials. Landiolol was generally well tolerated, with a relatively low risk of hypotension and bradycardia. It should be noted that the fast turnover of landiolol will diminish most adverse events due to self-limiting administration.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of landiolol in children has not been studied yet. Current available data (based on the treatment with Onoact) are insufficient to recommend adequate dosing for the paediatric population. In addition, there are not data from the use of Rapibloc in pregnant or breast-feeding women available. Current available data with the treatment of Onoact in pregnant women are limited.

VI.2.4 Summary of safety concerns

Rapibloc 300 mg / 600 mg powder for solution for infusion

Important identified risks

Risk	What is known	Preventability
Abnormally low blood pressure (Severe hypotension)	Landiolol may cause a low blood pressure – this may affect up to 1 in 10 people.	The physician is advised to continuously monitor the blood pressure and the ECG in all patients treated with landiolol. In the event of hypotension, landiolol dose should be reduced or the administration be discontinued and appropriate treatment should be provided as required.
Abnormally slow heart rate (Severe bradycardia)	Landiolol may cause a slow heart rate – this may affect up to 1 in 100 people.	The physician is advised to continuously monitor the ECG in all patients treated with landiolol. In the event of bradycardia, landiolol dose should be reduced or the administration be discontinued and appropriate treatment should be provided as required.
The heart does not pump enough blood (Cardiogenic shock)	Landiolol may cause a shock – this may affect up to 1 in 1,000 people.	The physician is advised that in case of a cardiogenic shock, the administration of landiolol should be discontinued and that these patients should receive appropriate medical management.
Heart conduction problems or cardiac arrest (Cardiac arrest, sinus arrest, complete AV block)	Landiolol may cause a cardiac arrest - this may affect up to 1 in 100 people. Landiolol may cause a sinus arrest - this may affect up to 1 in 1,000 people. Landiolol may cause a complete AV block (frequency cannot be estimated from the available data).	The physician is advised that in case of serious adverse reactions such as cardiac arrest, complete AV block or sinus arrest, the administration of landiolol should be discontinued and that these patients should receive appropriate medical management.

Risk	What is known	Preventability
Influence of medicines that affect heart conduction system and contractility and/or slow down the speed and volume of blood being pumped by the heart (Interaction with drugs affecting myocardial contractility and conduction, e.g. calcium antagonists such as verapamil and diltiazem; class I antiarrhythmic agents such as disopyramide, flecainide and propafenone; amiodarone;and digitalis preparations)	Concomitant use of landiolol with medicines that affect heart conduction system and contractility and/or slow down the speed and volume of blood being pumped by the heart may increase the risk of an abnormal low blood pressure and may result in suppression of cardiac function.	The physician is advised that administration of landiolol should be adjusted with caution and to monitor the patient's blood pressure and heart rate.
Influence of medicines used during surgery (Interaction with drugs used during anaesthesia, e.g. anaesthetics with bradycardic effect such as fentanyl citrate and propofol, esterase substrates such as procaine and suxamethonium, and cholinesterase inhibitors such as neostigmine)	Concomitant use of landiolol with medicines used during surgery may intensify the heart rate and blood pressure lowering effects or may prolong the action of landiolol.	The physician is advised that administration of landiolol should be adjusted with caution and to monitor the patient's blood pressure and heart rate.
Influence of medicines for the treatment of diabetes (Interaction with insulin or oral antidiabetic drugs leading to enhanced blood glucose lowering effect and masking of hypoglycaemic symptoms such as tachycardia)	Concomitant use of landiolol with medicines for the treatment of diabetes may intensify the blood sugar lowering effect. Landiolol may mask the symptom for a low blood sugar such as an increased heart rate.	The physician is advised to monitor blood sugar levels when landiolol is given concomitantly with antidiabetic drugs. The patients should be carefully monitored for early symptoms of low blood sugar levels.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Depression of myocardial contractility in patients with congestive heart failure leading to aggravation of heart failure	Landiolol belongs to a group of medicines called beta-blockers which influence heart conduction and pump action of the heart. In patients with heart failure the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body. Beta blockage carries a potential hazard for further worsening the pump action of the heart. Special caution should be taken if landiolol is administered in patients with heart failure.

Sudden increase in blood pressure in patients with untreated phaeochromocytoma	Phaeochromocytoma is an adrenal gland disease that may be accompanied by a sudden increase of blood pressure, severe headache, sweating and increased heartbeat. Landiolol may increase blood pressure when used in patients with untreated phaeochromocytoma. Patients with untreated phaeochromocytoma must not use landiolol.
Difficulty in breathing in patients with asthma and other diseases of narrowing of airways (Bronchospasms in patients with bronchospastic diseases)	Beta-blockers as a drug class can cause difficulties in breathing and wheezing due to its contractive effect on smooth muscles of the lung. This effect is triggered through the specific receptor beta-2. Landiolol is beta-1 receptor specific; however, since beta-1 selectivity of landiolol is not absolute these effects may occur. Landiolol should be used with caution in patients with bronchospastic diseases.
Aggravation of peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication)	Due to its contractive effect on blood vessels, beta-blockers in general may increase the risk of worsening of circulatory problems such as paleness of fingers or aching, tired and sometimes burning pains in the legs. Landiolol should be used with caution in such patients.
Allergic/anaphylactic reactions	In general, beta-blockers may increase the sensitivity toward the cause of the allergy and the intensity of strong allergic reactions. It is recommended that landiolol should be used with caution in patients with known allergies. Furthermore, patients with known allergies against landiolol or to other ingredients of the drug should not be treated with landiolol.

Risk	**What is known (Including reason why it is considered a potential risk)**
Medication errors	It should be noted that Rapibloc is available as two different formulations: • Rapibloc (Lyo) powder for solution for infusion containing 300 mg or 600 mg landiolol HCl per vial and • Rapibloc concentrate for solution for injection containing 20 mg / 2 ml landiolol HCl per ampoule. Incorrect reconstitution or dilutions of landiolol may result in severe accidental overdoses. These overdoses may result in death or permanent disability due to severe low blood pressure and heart rate followed by heart block and other severe reaction. Individual titration of the dosage of landiolol is of great importance. A starting dose is required followed by a maintenance dosage. The dose itself dependent on the body weight, sensitivity and medical background of the patient and other medications taken next to landiolol. To minimise both potential risks (i,e, wrong reconstitution/dilution and administration of the wrong volume), Rapibloc should only be administered by a health care professional.

Missing information

Risk	What is known
Limited information on use in children and adolescents (Paediatric population)	The safety and efficacy of landiolol in children aged 0 to 18 years have not yet been established. No recommendation on posology can be made from the data available.
Pregnancy and lactation	There are limited data from the use of landiolol in pregnant women available. Animal studies do not indicate direct or indirect harmful effects. As a precautionary measure, it is preferable to avoid the use of landiolol during pregnancy. It is unknown whether landiolol or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from landiolol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
possible influence of heparin on the plasma concentration of landiolol	Concomitant use of heparin may influence the action of landiolol in the body.

Rapibloc 20 mg/2 ml concentrate for solution for injection

Important identified risks

Risk	What is known	Preventability
Abnormally low blood pressure (Severe hypotension)	Landiolol may cause a low blood pressure – this may affect up to 1 in 10 people.	The physician is advised to continuously monitor the blood pressure and the ECG in all patients treated with landiolol. In the event of hypotension, additional doses of landiolol should be reduced or avoided and appropriate treatment should be provided as required.
Abnormally slow heart rate (Severe bradycardia)	Landiolol may cause a slow heart rate – this may affect up to 1 in 100 people.	The physician is advised to continuously monitor the ECG in all patients treated with landiolol. In the event of bradycardia, additional doses of landiolol should be reduced or avoided and appropriate treatment should be provided as required.
The heart does not pump enough blood (Cardiogenic shock)	Landiolol may cause a shock – this may affect up to 1 in 1,000 people.	The physician is advised that in case of a cardiogenic shock, no further landiolol doses should be administered and that these patients should receive appropriate medical management.

Heart conduction problems or cardiac arrest (Cardiac arrest, sinus arrest, complete AV block)	Landiolol may cause a cardiac arrest - this may affect up to 1 in 100 people. Landiolol may cause a sinus arrest - this may affect up to 1 in 1,000 people. Landiolol may cause a complete AV block (frequency cannot be estimated from the available data).	The physician is advised that in case of serious adverse reactions such as cardiac arrest, complete AV block or sinus arrest, no further landiolol doses should be administered and that these patients should receive appropriate medical management.

Risk	**What is known**	**Preventability**
Influence of medicines that affect heart conduction system and contractility and/or slow down the speed and volume of blood being pumped by the heart (Interaction with drugs affecting myocardial contractility and conduction, e.g. calcium antagonists such as verapamil and diltiazem; class I antiarrhythmic agents such as disopyramide, flecainide and propafenone; amiodarone; and digitalis preparations)	Concomitant use of landiolol with medicines that affect heart conduction system and contractility and/or slow down the speed and volume of blood being pumped by the heart may increase the risk of an abnormal low blood pressure and may result in suppression of cardiac function.	The physician is advised that administration of landiolol should be adjusted with caution and to monitor the patient's blood pressure and heart rate.
Influence of medicines used during surgery (Interaction with drugs used during anaesthesia, e.g. anaesthetics with bradycardic effect such as fentanyl citrate and propofol, esterase substrates such as procaine and suxamethonium, and cholinesterase inhibitors such as neostigmine)	Concomitant use of landiolol with medicines used during surgery may intensify the heart rate and blood pressure lowering effects or may prolong the action of landiolol.	The physician is advised that administration of landiolol should be adjusted with caution and to monitor the patient's blood pressure and heart rate.
Influence of medicines for the treatment of diabetes (Interaction with insulin or oral antidiabetic drugs leading to enhanced blood glucose lowering effect and masking of hypoglycaemic symptoms such as tachycardia)	Concomitant use of landiolol with medicines for the treatment of diabetes may intensify the blood sugar lowering effect. Landiolol may mask the symptom for a low blood sugar such as an increased heart rate.	The physician is advised to monitor blood sugar levels when landiolol is given concomitantly with antidiabetic drugs. The patients should be carefully monitored for early symptoms of low blood sugar levels.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Depression of myocardial contractility in patients with congestive heart failure leading to aggravation of heart failure	Landiolol belongs to a group of medicines called beta-blockers which influence heart conduction and pump action of the heart. In patients with heart failure the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body. Beta blockage carries a potential hazard for further worsening the pump action of the heart. Special caution should be taken if landiolol is administered in patients with heart failure.
Sudden increase in blood pressure in patients with untreated phaeochromocytoma	Phaeochromocytoma is an adrenal gland disease that may be accompanied by a sudden increase of blood pressure, severe headache, sweating and increased heartbeat. Landiolol may increase blood pressure when used in patients with untreated phaeochromocytoma. Patients with untreated phaeochromocytoma must not use landiolol.
Difficulty in breathing in patients with asthma and other diseases of narrowing of airways (Bronchospasms in patients with bronchospastic diseases)	Beta-blockers as a drug class can cause difficulties in breathing and wheezing due to its contractive effect on smooth muscles of the lung. This effect is triggered through the specific receptor beta-2. Landiolol is beta-1 receptor specific; however, since beta-1 selectivity of landiolol is not absolute these effects may occur. Landiolol should be used with caution in patients with bronchospastic diseases.
Aggravation of peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication)	Due to its contractive effect on blood vessels, beta-blockers in general may increase the risk of worsening of circulatory problems such as paleness of fingers or aching, tired and sometimes burning pains in the legs. Landiolol should be used with caution in such patients.
Allergic/anaphylactic reactions	In general, beta-blockers may increase the sensitivity toward the cause of the allergy and the intensity of strong allergic reactions. It is recommended that landiolol should be used with caution in patients with known allergies. Furthermore, patients with known allergies against landiolol or to other ingredients of the drug should not be treated with landiolol.

Risk	What is known (Including reason why it is considered a potential risk)
Medication errors	It should be noted that Rapibloc is available as two different formulations: • Rapibloc (Lyo) powder for solution for infusion containing 300 mg or 600 mg landiolol HCl per vial and • Rapibloc concentrate for solution for injection containing 20 mg / 2 ml landiolol HCl per ampoule. Incorrect dilutions of landiolol may result in severe accidental overdoses. These overdoses may result in death or permanent disability due to severe low blood pressure and heart rate followed by heart block and other severe reaction. Individual titration of the dosage of landiolol is of great importance. A starting dose is required followed by a maintenance dosage. The dose itself dependent on the body weight and the medical background of the patient and other medications taken next to landiolol. To minimise both potential risks, Rapibloc should only be administered by a health care professional.

Missing information

Risk	What is known
Limited information on use in children and adolescents (Paediatric population)	The product contains ethanol and is therefore not recommended for the use in the paediatric population.
Pregnancy and lactation	There are limited data from the use of landiolol in pregnant women available. Animal studies do not indicate direct or indirect harmful effects. As a precautionary measure, it is preferable to avoid the use of landiolol during pregnancy. It is unknown whether landiolol or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from landiolol therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
possible influence of heparin on the plasma concentration of landiolol	Concomitant use of heparin may influence the action of landiolol in the body.

VI.2.5 Summary of risk minimisation measures by safety concern

All important identified and potential risks are adequately addressed in the 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

There are no studies planned.

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

Not applicable.