Perindopril 2 mg, 4 mg and 8 mg

Date: 27-Mar-2017, Version 1.2

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Hypertension is a condition in which the blood pressure is too high. Hypertension is usually "essential" when the hypertension has no obvious cause. High blood pressure increases the workload of the heart and arteries. If this continues for a long time, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure, heart attack or kidney failure. Lowering the blood pressure to a normal level reduces the risk of developing these disorders.

Diseases of the heart and circulatory system (cardiovascular disease [CVD]) are the main cause of death in Europe accounting for over 4 million deaths each year. The main forms of CVD are coronary heart disease (CHD) and stroke. CHD by itself is the single most common cause of death in Europe: accounting for 1.8 million deaths in Europe each year. Over one in five women (22 %) and one in five men (20 %) die from the disease[1].

VI.2.2 Summary of treatment benefits

Perindopril belongs to a class of medicines called angiotensin-converting enzyme (ACE) inhibitors.

ACE inhibitors like perindopril prevent creation of a hormone called as angiotensin II by blocking a chemical called as ACE. This widens the blood vessels and helps to reduce the amount of water put back into the blood by kidneys. This action decreases the blood pressure in patients having high blood pressure, improves the functioning of the heart, and thereby prevents complications like heart attack or stroke.

VI.2.3 Unknowns relating to treatment benefits

Clinical studies have not been conducted in children and adolescents less than 18 years old and in breast-feeding females.

VI.2.4 Summary of safety concerns

Table 11: Important identified risks

Risk in Lay Language (Clinical Term)	**What is known**	**Preventability**
Allergic reactions that cause swelling of eyelids, face, lips, tongue or throat, which can cause great difficulty in breathing and serious allergic reactions **(Hypersensitivity reactions including angioedema)**	Swelling of eyelids, face, lips, tongue or throat are uncommon side effects with perindopril (seen between 1 and 10 patients in 1000). Sometimes serious allergic reactions may also occur which may be life threatening.	In such cases, Perindopril should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred.
High level of potassium in the blood **(Hyperkalaemia)**	High level of potassium in the blood is an uncommon side effect with perindopril (seen between 1 and 10 patients in 1000). This may cause serious, sometimes fatal, irregular heartbeat.	Yes by following the special warnings and precautions for use and the interactions with other medicinal products.

[1] European Cardiovascular Disease Statistics. 2012 Edition.

Risk in Lay Language (Clinical Term)	What is known	Preventability
Harm to unborn child when used during the second and third trimesters of pregnancy **(Foetotoxicity (2nd – 3rd trimester))**	Perindopril may cause serious harm to baby if used after the third month of pregnancy.	Yes by following the contraindication of perindopril after 3 months of pregnancy. Patients must tell their doctor if patients become pregnant.
Decreased production of certain blood cells e.g. white blood cells or platelets **(Neutropenia/agranulocytosis/ thrombocytopenia)**	Disorders of the blood are very rare side effects with perindopril (seen in less than 1 patient in 10,000).	Periodic monitoring of white blood cells is advised. Patients are instructed to report any sign of infection e.g.sore throat, fever.
Blockade of important regulator of blood pressure as well as fluid and electrolyte balance, plays an important role in the pathophysiology of cardiovascular and kidney diseases. **(Dual blockade of the renin-angiotensinaldosterone system (RAAS))**	Concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy	Yes by following the special warnings and precautions for use and the interactions with other medicinal products.

Table 12: Important potential risks

Risk in Lay Language (Clinical Term)	What is known
Harm to unborn child when used during the first trimester of pregnancy **(Teratogenicity (with use in first trimester of pregnancy))**	Perindopril is not recommended during the first 3 months of pregnancy. Patients must tell their doctor if they think they are (or might become) pregnant.

Table 13: Missing information

Risk in Lay Language (Clinical Term)	What is known
Use in children and adolescents < 18 years **Use during breast-feeding (lactation)**	The efficacy and safety of perindopril has not been studied in this population. The efficacy and safety of perindopril has not been studied in this population.

VI.2.5 Summary of risk minimisation measures by safety concern

Summary of Product Characteristics (SmPC) of perindopril, provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them.

This medicinal product has no additional risk minimisation measures for any of mentioned safety concerns.

VI.2.6 Planned post authorisation development plan
No post authorisation study is planned for this product.

VI.2.7 Summary of changes to the Risk Management Plan over time
The changes to RMP are presented in the table below.

Version	Date	Safety Concerns	Comments
1	16-Sep-2016	Important Identified Risks 1. Hypersensitivity reactions including angioedema, intestinal angioedema, Anaphylactoid and Anaphylactic reactions 2. Renal impairment (including renal failure) 3. Hyperkalaemia 4. Hypotension (symptomatic) 5. Foetotoxicity - /use during second and third trimesters of pregnancy 6. Neutropenia/agranulocytosis/ thrombocytopenia Important Potential Risks 1. Use during first trimester of pregnancy Missing Information 1. Exposure in children and adolescents < 18 years 2. Use during breast-feeding (Lactation)	First version of the RMP.
1.1	12-Oct-2016	Addition of safety concerns - Exacerbation of psoriasis (Important identified risk) - Drug interactions with mTOR inhibitors (Important potential risk)	The list of safety concerns was updated based on the PRAC recommendations (EMA/528822/2016) dated 22 Jun 2016. Inclusion all dosage strengths of Perindopril (2 mg, 4 mg, and 8 mg).
1.2	27-Mar-2017	**Following safety concerns were deleted:** **Important identified risks:** • Renal impairment (including renal failure) • Hypotension (symptomatic) • Exacerbation of psoriasis **Important potential risks:** • Drug interactions with mTOR inhibitors **Following safety concerns were modified:** **Important identified risks** • "Hypersensitivity reactions incl. angioedema and intestinal angioedema, anaphylactoid and anaphylactic reactions" changed to "Hypersensitivity reactions including angioedema"	Safety concerns are aligned based on Day 40 comments from the RMS. Information regarding the updated safety concerns aligned to respective sections of the RMP. Text in Part III revised based on updated Glenmark template. Minor grammatical and formatting changes done in the RMP.

Version	Date	Safety Concerns	Comments
		• "Foetotoxicity - /use during second and third trimesters of pregnancy" changed to "Foetotoxicity (2nd – 3rd trimester)" • "Exacerbation of psoriasis" changed to "Dual blockade of the renin-angiotensinaldosterone system (RAAS)" **Important potential risks** • "Teratogenicity (with use in first trimester of pregnancy)" changed to "Use during first trimester of pregnancy" **Missing information** • "Exposure in children and adolescents < 18 years" changed to "Use in children and adolescents < 18 years"	