Part VI: Summary of the risk management plan for Lisinopril

This is a summary of the risk management plan (RMP) for lisinopril**.** The RMP details important risks of lisinopril, how these risks can be minimised, and uncertainties (missing information).

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

I. The medicine and what it is used for

Lisinopril Antibiotice is authorised for treatment of essential hypertension, chronic stable angina pectoris and chronic heart failure.

It contains lisinoprilum as the active substance and it is given by oral route.

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

Important risks of Lisinopril Antibiotice, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified are:

- 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 medicine's legal status - Prescription product.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, routine pharmacovigilance activities including adverse reactions reporting, PSUR, medical literature monitoring, and other activities as required under EU legislation, are made.

No additional risk minimisation measures are proposed.

No missing information is proposed.

II. A. List of important risks and missing information

Important risks of Lisinopril Antibiotice, 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 Lisinopril Antibiotice. 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 (paediatric patients, use during breastfeeding, use in patients who have recently undergone renal transplantation).

Summary of safety concerns	
Important identified risks	1. Hypersensitivity reactions and angioedema 2. Foetotoxicity and neonatal toxicity when used in 2nd and 3rd trimesters of pregnancy
Important potential risks	-
Missing information	-

II. B. Summary of important risks

The safety information in the Product Information is aligned to the reference medicinal product – Zestril® tablets, Astra Zeneca.

Important identified risks

Important identified risks: Hypersensitivity reactions and angioedema	
Evidence for linking the risk to the medicine	Evidence is based on literature data from clinical studies and case reports. *Johanna L. Norman, Whitney L. Holmes et al. presented in 2012* the case of a 65-year-old African American woman who experienced 2 episodes of angioedema, with the second being life threatening after receiving several concomitant agents known to cause angioedema, most notably lisinopril for 11 years. *Johannes Ring in 2002* presented the case of a 75-year-old Afro-Caribbean man presented with marked tongue swelling developing over several hours. The patient's history included ischemic heart disease and hypertension, for which he was taking lisinopril. There was no history or family history of angioedema.
Risk factors and risk groups	The increased risk in black patients may be related to racial differences in the kallikrein-kinin system and increased sensitivity to bradykinin. Nevertheless, it remains unclear why bradykinin induces angioedema in only a small fraction of patients on ACEI medication most notably after a considerable period of uneventful treatment, whereas the vast majority of patients never encounter this side-effect. Although an increased plasma bradykinin level appears to play a significant role in the course of ACEI-induced angioedema, additional factors are likely involved in the underlying pathological process. *(M. Bas et al. 2004)*
Risk minimisation measures	- In section 4.3 of the SmPC and PL section 2 contraindication on use in patients with hypersensitivity to lisinopril or to any other angiotensin converting enzyme (ACE) inhibitor is stated. Also, contraindication on use in patients with history of angioedema is included in the same sections. -Warnings on reported hypersensitivity/angioedema reactions any time during treatment and recommendation on therapy which should be administered promptly until complete resolution of symptoms are listed in in section 4.4 of the SmPC and PL section 2. In section 4.5 of SmPC is stated the increase risk of angioedema in association with specific concomitant medication such as mTOR inhibitors, vildagliptin or neprilysin (NEP) inhibitors, sacubitril/valsartan. -In PL section 2 is contraindicated the use of medicines concomitant with other medicines associated with an increased risk of adverse reaction (angioedema). Other routine risk minimisation measures beyound the Product Information: Prescription only product.
Additional pharmacovigilance activities	NA

Important identified risks: Foetotoxicity and neonatal toxicity when used in 2nd and 3rd trimesters of pregnancy	
Evidence for linking the risk to the medicine	Evidence is based on literature data from clinical studies and case reports.

	Second- and third-trimester exposure to ACE inhibitors seems to carry an Important. but as yet unquantified. risk of fetotoxicity, resulting in major morbidity and mortality. Emphasis on this distinction is important because of the indisputable therapeutic usefulness of the drugs of this class and the potentiality that women will conceive while taking one of them. *Peter G. Pryde et al. (1993)*
Risk factors and risk groups	Risk factors and risk groups women in the second and third trimester of pregnancy.
Risk minimisation measures	- Warnings on possibility to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) after exposure to ACE inhibitor therapy during the second and third trimesters is stated in section 4.6 of the SmPC and PL section 2. In section 4.6 and 5.3 of the SmPC is included warning regarding ACE inhibitor therapy exposure during the second and third trimesters and relationship with human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Also, are mentioned the measures needed after the exposure to ACE inhibitor in the second trimester of pregnancy - ultrasound check of renal function and skull, newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. In section 2 of PL there is a warning that lisinopril is not recommended in the first trimester of pregnancy along with the recommendation of the announcement of the intention or the probability of being pregnant. Also, is stated the contraindication of lisinopril's use in the last 6 months of pregnancy. Other routine risk minimisation measures beyound the Product Information: Prescription only product.
Additional pharmacovigilance activities	NA

Important potential risks

Not available

Missing information

Not available

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