Part VI: Summary of the risk management plan

Summary of risk management plan for Triplixam/Arplexam

This is a summary of the risk management plan (RMP) for Triplixam/Arplexam. The RMP details important risks of Triplixam/Arplexam and how more information will be obtained about Triplixam/Arplexam's risks and uncertainties (missing information).

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

Important new concerns or changes to the current ones will be included in updates of Triplixam/Arplexam's RMP.

I. The medicine and what it is used for

Triplixam/Arplexam is authorised for substitution therapy for treatment of essential hypertension, in patients already controlled with perindopril/indapamide fixed dose combination and amlodipine, taken at the same dose level. It contains perindopril, indapamide and amlodipine as the active substances and it is given by oral route.

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

Important risks of Triplixam/Arplexam, together with measures to minimise such 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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Triplixam/Arplexam is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Triplixam/Arplexam are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Triplixam/Arplexam. 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	Hypotension (including increased risk of hypotension when combining RAS agents) Renal failure (including increased risk of renal failure when combining RAS agents) Hypokalaemia Hyperkalaemia (including increased risk of hyperkalaemia when combining RAS agents) Neutropenia/agranulocytosis/thrombocytopenia Foetotoxicity/use during 2nd and 3rd trimesters of pregnancy Angioedema Anaphylactoid reactions Photosensitivity Hepatitis (including hepatic encephalopathy fulminant hepatitis) Myocardial infarction Arrhythmia Pancreatitis
Important potential risks	Use during first trimester of pregnancy Pulmonary oedema in patients with heart failure
Missing information	Children and adolescent

II.B Summary of important risks

Important identified risk: Hypotension (including increased risk of hypotension when combining RAS agents)	
Evidence for linking the risk to the medicine	Hypotension and effects related to hypotension are listed for each of the mono-components of perindopril/ indapamide/ amlodipine FDC (common for perindopril, uncommon for amlodipine, and very rare for indapamide); hypotension is thus more likely to occur with the fixed dose combination combining products having complementary mode of action on blood pressure control.

Risk factors and risk groups	Known risk groups/risk factors include: - patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney; treatment with diuretics may be a contributory factor, - patients who have been volume- and sodium depleted (by prolonged diuretic therapy, dietary salt restriction, diarrhoea or vomiting), in particular individuals with renal artery stenosis, - patients with congestive heart failure or cirrhosis with oedema and ascites, - dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren, - concomitant therapy with baclofen, non-potassium sparing diuretics, strong or moderate CYP3A4 inhibitors (clarithromycin), imipramine-like antidepressants (tricyclic), neuroleptics, other antihypertensive agents and vasodilators; concomitant use of certain anaesthetic drugs, gold, and concomitant intake of grapefruit or grapefruit juice.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with severe hypotension is stated in section 4.3 of the SmPC. - A contraindication in patients with significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is stated in section 4.3 of the SmPC. - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension. - A precaution for use in section 4.4 of the SmPC concerns hypotension and water and sodium depletion and recommendation for plasma electrolytes monitoring.

	- A warning in section 4.4 of the SmPC states that the risk of hypotension increases in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney. - A precaution for use in section 4.4 of the SmPC concerns the use of Triplixam in case of Atherosclerosis. - There is a precaution for use in section 4.4 of the SmPC concerning Surgery / anaesthesia. - Concomitant uses which could increase the risk of hypotension are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with severe low blood pressure. The blood pressure may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Renal failure (including increased risk of renal failure when combining RAS agents)	
Evidence for linking the risk to the medicine	Renal failure is listed for two of the mono-components of perindopril/ indapamide/ amlodipine FDC (uncommon for perindopril, very rare for indapamide); acute renal failure is listed for perindopril with a frequency very rare. Perindopril and indapamide mono-components can decrease glomerular filtration rate by different mechanisms, thus their effects can add on in the FDC.
Risk factors and risk groups	Known risk groups/risk factors include: - patients with underlying renal failure including renal artery stenosis, - patients with water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), patients with initially low blood pressure, patients with renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites, - dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren,concomitant treatment with non-potassium-sparing and potassium-sparing diuretics, non-steroidal anti-inflammatory medicinal products

	(included acetylsalicylic acid at high doses), - concomitant use of iodinated contrast media, ciclosporine.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with severe renal impairment (creatinine clearance below 30 mL/min) is stated in section 4.3 of the SmPC. - A contraindication in patients with moderate renal impairment (creatinine clearance below 60 mL/min) is stated in section 4.3 of the SmPC of Triplixam for doses containing 10mg/2.5mg of perindopril/indapamide combination. - A contraindication concerning the concomitant use with aliskiren-containing products in patients with renal impairment (GFR < 60mL/min/1.73m2) is stated in section 4.3 of the SmPC. - A contraindication in patients with significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is stated in section 4.3 of the SmPC. - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of decreased renal function. - A warning in section 4.4 of the SmPC states that the risk of renal insufficiency increases in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney. - Precautions for use in case of renal impairment are stated in section 4.4 of the SmPC. - Recommendations for Renal function testing in the elderly are detailed in section 4.4 and 5.2 of the SmPC. - Concomitant uses which could increase the risk of renal failure and recommendations concerning renal function monitoring are detailed in section 4.5 of the SmPC.

	- According to section 2 of the PIL, product must not be used in patients with severe kidney disease, renal artery stenosis and in case of concomitant use with aliskiren-containing products in patients with renal impairment. The kidney function may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Hypokalaemia	
Evidence for linking the risk to the medicine	Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The combination of indapamide with perindopril and amlodipine does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure.
Risk factors and risk groups	Known risk groups/risk factors include: - elderly (>65yrs) and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure, - increased potassium excretion due to vomiting or diarrhoea, - concomitant treatment with drugs that increase the risk of hypokalaemia such as loop diuretics, thiazides or thiazide-like diuretics, amphotericin B, systemic glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypokalaemia is stated in section 4.3 of the SmPC. - A precaution for use concerning the risk of hypokalaemia and recommendations for the monitoring of plasma potassium are detailed in section 4.4 of the SmPC.

	- Concomitant uses which could increase the risk of hypokalaemia and recommendations concerning plasma potassium monitoring are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with low plasma potassium levels and the amount of potassium in blood may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Hyperkalaemia (including increased risk of hyperkalaemia when combining RAS agents)	
Evidence for linking the risk to the medicine	Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Hyperkalaemia reversible on discontinuation is listed with a frequency uncommon for perindopril mono-component of perindopril/ indapamide/ amlodipine FDC.
Risk factors and risk groups	Risk groups/factors for the development of hyperkalaemia include: - patients with renal insufficiency, worsening of renal function, - age (> 70 years), - diabetes mellitus, - intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, - concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; particularly in patients with impaired renal function (may lead to a significant increase in serum potassium), - patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, aliskiren, other ACE inhibitors, angiotensin-II antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus),

	- concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren (dual blockade of the renin-angiotensin-aldosterone system (RAAS).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hyperkalaemia. - Concomitant uses which could increase the risk of hyperkalaemia and recommendations concerning the monitoring of serum potassium are detailed in section 4.5 of the SmPC. - There is a warning concerning the use of salt substitutes which contain potassium and medicines which should be avoided are detailed in section 2 of the PIL. The amount of potassium in blood may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Neutropenia/agranulocytosis/thrombocytopenia	
Evidence for linking the risk to the medicine	Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Neutropenia has been observed during treatment with perindopril (very rare). Agranulocytosis has been observed during treatment with perindopril and indapamide (very rare). Thrombocytopenia has been observed during treatment with perindopril, amlodipine and indapamide with a frequency of very rare (SmPCs of mono-components).
Risk factors and risk groups	Patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function.

Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC stating that neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Foetotoxicity/use during 2nd and 3rd trimesters of pregnancy	
Evidence for linking the risk to the medicine	Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (Perindopril SmPC) The prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation (Indapamide SmPC).
Risk factors and risk groups	Women of childbearing potential. Pregnant women during the second or third trimester.
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication during the second and third trimester of pregnancy, is stated in sections 4.3 and 4.6 of the SmPC. - A warning concerning pregnancy is stated in section 4.4 of the SmPC.

	- In addition in section 4.6 of the SmPC is stated that exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). It is also stated that prolonged exposure to thiazide may cause a feto-placental ischemia and growth retardation. - According to section 2 of the PIL, product must not be used in patients who are more than 3 months pregnant. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Angioedema	
Evidence for linking the risk to the medicine	Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and / or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril. This may occur at any time during therapy. Angioedema associated with laryngeal oedema may be fatal. Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal.
Risk factors and risk groups	Known risk groups/risk factors include: - patients with a history of angioedema unrelated to ACE inhibitor therapy, - black patients (black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks), - concomitant use with estramustine, gliptins ((linagliptine, saxagliptine, sitagliptine, vildagliptine), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus), racecadotril, sacubitril/ valsartan.

Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, to other sulfonamides or to any of the excipients is stated in section 4.3 of the SmPC. - A contraindication in patients with history of angioedema associated with previous ACE inhibitor therapy is stated in section 4.3 of the SmPC. - A contraindication in patients with hereditary/idiopathic angioedema is stated in section 4.3 of the SmPC. - A contraindication in case of concomitant use with sacubitril/valsartan is stated in section 4.3 of the SmPC. - In addition there is a warning in section 4.4 of the SmPC stating that ACE inhibitors may cause angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and / or larynx as well as intestinal angioedema. - Concomitant uses which could increase the risk of angioedema are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients who have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema). In this section is also stated that in case of swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing treatment must be stopped immediately. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Anaphylactoid reactions	
Evidence for linking the risk to the medicine	There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor (Perindopril SmPC).
Risk factors and risk groups	Allergic patients treated with desensitisation, patients undergoing venom immunotherapy, patients undergoing low density lipoprotein (LDL)-apheresis, haemodialysis patients dialysed with high-flux membranes (e.g., AN 69®).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, to other sulfonamides or to any of the excipients is stated in section 4.3 of the SmPC. - A contraindication in case of extracorporeal treatments leading to contact of blood with negatively charged surfaces is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning anaphylactoid reactions during desensitization.

	- In addition, there are warnings in section 4.4 of the SmPC of Triplixam concerning anaphylactoid reactions during LDL apheresis and anaphylactoid reactions in haemodialysis patients. - Concomitant uses which could increase the risk of anaphylactoid reactions are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients who are receiving dialysis or any other type of blood filtration. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Photosensitivity	
Evidence for linking the risk to the medicine	Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. Photosensitivity reaction has been observed with the treatment of perindopril (uncommon), amlodipine (very rare) and indapamide (not known) (SmPC §4.8).
Risk factors and risk groups	Risk factor is exposure to the sun or to artificial UVA. In vivo and in vitro studies have indicated that UV-B and UV-A radiation could have additive or even synergistic effects (Gómez-Bernal; 2014).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC concerning photosensitivity reactions which have been reported with thiazides and thiazide-related diuretics. - There is a warning in section 2 of the PIL, stating that patients have to talk to their doctor if they have had photosensitivity reactions.

	Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Hepatitis (including hepatic encephalopathy fulminant hepatitis)	
Evidence for linking the risk to the medicine	Hepatitis and possibility of onset of hepatic encephalopathy in case of hepatic insufficiency are listed with a frequency 'not known' (Indapamide SmPC). Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up. Hepatitis either cytolitic or cholestatic is listed with a frequenc 'very rare' (Perindopril SmPC). Hepatitis, jaundice, hepatic enzyme increased mostly consistent with cholestasis have been observed during the treatment with amlodipine (very rare) (Amlodipine SmPC).
Risk factors and risk groups	Risk factors according to the Guidelines of American College of Gastroenterology (ACG) – Variables that may predispose individuals to idiosyncratic DILI (3 categories) (Chalasani; 2014): Host factors: - Age (probably because the elderly receive multiple drugs and have low tolerability), - Gender female, - Pregnancy, - Malnutrition, - Obesity, - Diabetes mellitus, - Co-morbidities including underlying liver disease, - Indications for therapy. Environmental factors: - Smoking, - Alcohol consumption, - Infection and inflammatory episodes.

	Drug-related factors: - Daily dose, - Metabolic profile, - Class effect and cross-sensitization, - Drug interaction and polypharmacy. Predisposing factors for the development of hepatic encephalopathy are alcohol consumption, high levels of ammonia, zinc and branched chain amino acids, the presence of esophageal varices, and minimal hepatic encephalopathy. Electrolyte abnormalities, bleeding into the gastrointestinal tract, infections, high protein diet, diuretics, and sedatives may stimulate the development of hepatic encephalopathy (Ciećko-Michalska; 2012).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hepatic encephalopathy and severe hepatic impairment is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning hepatic impairment. - According to section 2 of the PIL, product must not be used in patients who have severe liver disease or suffer from a condition called hepatic encephalopathy. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Myocardial infarction	
Evidence for linking the risk to the medicine	Myocardial infarction (possibly secondary to excessive hypotension in high risk patients) has been observed during the treatment with perindopril (very rare) and amlodipine (very rare) (SmPCs of mono-components).

Risk factors and risk groups	Known cardiovascular risk factors and risk modifiers include advanced age, gender, physical activity, smoking (current and former), high risk diet, overweight (abdominal obesity), diabetes, hypertension, hyperlipidaemia, socio-economic status, family history of premature cardio-vascular disease. Clinical conditions affecting cardiovascular disease risk include chronic kidney disease, autoimmune diseases, obstructive sleep apnoea syndrome (Piepoli; 2016). Risk groups include patients with ischaemic heart or cerebrovascular disease presenting risk factors for hypotension (see section SVII.3.1), patients with congestive heart failure, severe hypertension (including forms of hypertrophic obstructive cardiomyopathy), and severe aortic valve stenosis, patients with other cardiac valvular pathologies and low cardiac output states associated with a decreased mean aortic pressure, which is the prime component of coronary perfusion pressure.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with haemodynamically unstable heart failure after acute myocardial infarction is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning the risk of myocardial infarction which be leaded by an excessive fall in blood pressure. - According to section 2 of the PIL, product must not be used in patients who are suspected of having untreated decompensated heart failure and suffer from heart failure after a heart attack. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Arrhythmia	
Evidence for linking the risk to the medicine	Arrhythmia has been observed during the treatment with perindopril and indapamide (very rare); arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) has been observed during the treatment with amlodipine (uncommon). Electrocardiogram QT prolonged and torsade de pointes has been observed with indapamide (not known) (SmPCs of mono-components).
Risk factors and risk groups	Known risk factors of arrhythmia include structural heart disease: coronary heart disease, valvular disease, cardiomyopathy, heart failure, prior heart surgery, congenital heart disease, hypertension, left ventricular hypertrophy, thyroid hyper- or hypofunction, diabetes, obstructive sleep apnoea, electrolyte disorders, use of caffeine or other stimulants. Risk factors for ECG QT prolonged (Barnay; 2006); (Letsas; 2009) include: - Advanced age (> 60 years), - Female gender, - Bradycardia with sinus node dysfunction or atrioventricular block, Electrolytes abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), - Cardiac diseases such as ischemia, myocarditis, dilated or hypertrophiccardiomyopathy, - Severe nutritional disorders (anorexia nervosa, cachexia, celiac disease), - Metabolic processing of pharmacological agents by cytochrome P450, - Other treatment known to induce QT prolonged. Risk factors for Torsade de pointes include (Gupta; 2007): - Female gender, - Structural heart disease: myocardial infarction, heart failure, valvular disease or cardiomyopathy, - Hypokalaemia, - Multiple QT prolonging drugs or agents interfering with their metabolism, - Prolonged baseline QT (drugs or agenFamily history of congenital long QT syndrome, - Prior drug-induced torsade de pointes,

	- Bradycardia, - Atrioventricular block.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypokalaemia is stated in section 4.3 of the SmPC. - Precautions for use concerning the risks of arrhythmias and recommendations for serum potassium monitoring are detailed in section 4.4 of the SmPC. - Concomitant uses which could increase the risk of arrhythmias and recommendations concerning the monitoring of serum potassium are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with low plasma potassium levels and the amount of potassium in blood may be checked by the doctor. Product must not be used in patients taking non antiarrhythmic medicines causing life-threatening irregular beat. Patients have to talk to their doctor if they have any heart rhythm problems. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important identified risk: Pancreatitis	
Evidence for linking the risk to the medicine	Pancreatitis has been observed during the treatment with perindopril, indapamide, amolodipine (very rare) (SmPCs of mono-components).
Risk factors and risk groups	Risk groups/risk factors include: - Biliary tract disease, - Alcohol use, - Endoscopic retrograde cholangiopancreatography,

	- Abdominal trauma, - Developmental abnormalities of the pancreas (annular pancreas, pancreas divisum, sphincter of Oddi dysfunction), - Hypercalcemia (excessive vitamin D therapy, hyperparathyroidism, total parenteral nutrition), - Hypertriglyceridemia, - Tumors of pancreas, - Autoimmune disorders, - Type 2 diabetes, - Obesity (abdominal adiposity): the association is more important in patients with a waist circumference > 105 cm than in patients with a BMI > 30 kg.m2, - Smocking (Frossard; 2008); (Sadr-Azodi; 2012); (Sadr-Azodi; 2013); (Noel; 2009); (Girman; 2010).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important potential risk: Use during first trimester of pregnancy	
Evidence for linking the risk to the medicine	This risk is related to perindopril mono-component of the combination. Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.
Risk factors and risk groups	Women of childbearing potential, pregnant women during the first trimester.
Risk minimisation measures	Routine risk communication: - None

	Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC stating that when pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately. In addition, in section 4.6 it is stated that given the effects of the individual components in this combination product on pregnancy and lactation, bisoprolol/perindopril/amlodipine is not recommended during the first trimester of pregnancy. - According to section 2 of the PIL, patients should inform their doctors if they think they are (or might become) pregnant as product is not recommended in the early pregnancy. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Important potential risk: Pulmonary oedema in patients with heart failure	
Evidence for linking the risk to the medicine	In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group.
Risk factors and risk groups	Patients with heart failure, especially severe heart failure (NYHA III and IV).
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - A precaution for use in section 4.4 of the SmPC of Triplixam states that the incidence of pulmonary oedema could increase in patients with severe heart failure when they are treated by amlodipine. - According to section 2 of the PIL, product must not be used in patients who are suspected of having untreated decompensated heart failure and suffer from heart failure after a heart attack.

	Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

Missing information: Children and adolescent	
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a mention in section 4.2 of the SmPC stating that the safety and efficacy of product in children and adolescents have not been established. - In addition, there is a mention in section 5.1 of the SmPC stating that no data are available in children. - According to section 2 of the PIL, the use of product is not recommended in children and adolescents. - According to section 5 of the PIL, this medicine has to be kept out of the sight and reach of children. Other routine risk minimisation measures beyond the Product Information: - Legal status: Restricted medical prescription medicine.

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 Triplixam/Arplexam.

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

There are no studies required for Triplixam/Arplexam.

Summary of risk management plan for Viacorlix

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

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

Important new concerns or changes to the current ones will be included in updates of Viacorlix's RMP.

I. The medicine and what it is used for

Viacorlix is authorised for substitution therapy for treatment of essential hypertension, in adult patients already controlled with perindopril/amlodipine fixed dose combination and indapamide, taken at the same dose level. It contains perindopril, amlodipine and indapamide as the active substances and it is given by oral route.

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

Important risks of Viacorlix, together with measures to minimise such 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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Viacorlix is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Viacorlix are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Viacorlix. 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	Hypotension (including increased risk of hypotension when combining RAS agents) Renal failure (including increased risk of renal failure when combining RAS agents) Hypokalaemia Hyperkalaemia (including increased risk of hyperkalaemia when combining RAS agents) Neutropenia/agranulocytosis/thrombocytopenia Foetotoxicity/use during 2nd and 3rd trimesters of pregnancy Angioedema Anaphylactoid reactions Photosensitivity Hepatitis (including hepatic encephalopathy fulminant hepatitis) Myocardial infarction Arrhythmia Pancreatitis
Important potential risks	Use during first trimester of pregnancy Pulmonary oedema in patients with heart failure
Missing information	Children and adolescent

II.B Summary of important risks

Important identified risk: Hypotension (including increased risk of hypotension when combining RAS agents)	
Evidence for linking the risk to the medicine	Hypotension and effects related to hypotension are listed for each of the mono-components of perindopril/ indapamide/ amlodipine FDC (common for perindopril, uncommon for amlodipine, and very rare for indapamide); hypotension is thus more likely to occur with the fixed dose combination combining products having complementary mode of action on blood pressure control.

Risk factors and risk groups	Known risk groups/risk factors include: - patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney; treatment with diuretics may be a contributory factor, - patients who have been volume- and sodium depleted (by prolonged diuretic therapy, dietary salt restriction, diarrhoea or vomiting), in particular individuals with renal artery stenosis, - patients with congestive heart failure or cirrhosis with oedema and ascites, - dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren, - concomitant therapy with baclofen, non-potassium sparing diuretics, strong or moderate CYP3A4 inhibitors (clarithromycin), imipramine-like antidepressants (tricyclic), neuroleptics, other antihypertensive agents and vasodilators; concomitant use of certain anaesthetic drugs, gold, and concomitant intake of grapefruit or grapefruit juice.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with severe hypotension is stated in section 4.3 of the SmPC. - A contraindication in patients with significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is stated in section 4.3 of the SmPC. - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension. - A precaution for use in section 4.4 of the SmPC concerns hypotension and water and sodium depletion and recommendation for plasma electrolytes monitoring.

	- A warning in section 4.4 of the SmPC states that the risk of hypotension increases in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney. - There is a precaution for use in section 4.4 of the SmPC concerning Surgery / anaesthesia. - Concomitant uses which could increase the risk of hypotension are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with severe low blood pressure. The blood pressure may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Renal failure (including increased risk of renal failure when combining RAS agents)	
Evidence for linking the risk to the medicine	Renal failure is listed for two of the mono-components of perindopril/ indapamide/ amlodipine FDC (uncommon for perindopril, very rare for indapamide); acute renal failure is listed for perindopril with a frequency very rare. Perindopril and indapamide mono-components can decrease glomerular filtration rate by different mechanisms, thus their effects can add on in the FDC.
Risk factors and risk groups	Known risk groups/risk factors include: - patients with underlying renal failure including renal artery stenosis, - patients with water and electrolyte depletions (strict sodium restricted diet or prolonged diuretic treatment), patients with initially low blood pressure, patients with renal artery stenosis, congestive heart failure or cirrhosis with oedema and ascites, - dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren,concomitant treatment with non-potassium-sparing and potassium-sparing diuretics, non-steroidal anti-inflammatory medicinal products (included acetylsalicylic acid at high doses),

	- concomitant use of iodinated contrast media, ciclosporine.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with severe renal impairment (creatinine clearance below 30 mL/min) is stated in section 4.3 of the SmPC. - A contraindication concerning the concomitant use with aliskiren-containing products in patients with renal impairment (GFR < 60mL/min/1.73m2) is stated in section 4.3 of the SmPC. - A contraindication in patients with significant bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney is stated in section 4.3 of the SmPC. - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of decreased renal function. - A warning in section 4.4 of the SmPC states that the risk of renal insufficiency increases in patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney. - Precautions for use in case of renal impairment are stated in section 4.4 of the SmPC. - Recommendations for Renal function testing in the elderly are detailed in section 4.4 and 5.2 of the SmPC. - Concomitant uses which could increase the risk of renal failure and recommendations concerning renal function monitoring are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with severe kidney disease, renal artery stenosis and in case of concomitant use with aliskiren-containing products in patients with renal impairment. The kidney function may be checked by the doctor.

	Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Hypokalaemia	
Evidence for linking the risk to the medicine	Potassium depletion with hypokalaemia is a major risk with thiazide diuretics and thiazide-related diuretics. The combination of indapamide with perindopril and amlodipine does not prevent the onset of hypokalaemia particularly in diabetic patients or in patients with renal failure.
Risk factors and risk groups	Known risk groups/risk factors include: - elderly (>65yrs) and/or malnourished subjects, whether or not they are taking multiple medications, cirrhotic patients with oedema and ascites, coronary patients and patients with heart failure, - increased potassium excretion due to vomiting or diarrhoea, - concomitant treatment with drugs that increase the risk of hypokalaemia such as loop diuretics, thiazides or thiazide-like diuretics, amphotericin B, systemic glucocorticoids and mineralocorticoids (systemic route), tetracosactide, stimulant laxatives.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypokalaemia is stated in section 4.3 of the SmPC. - A precaution for use concerning the risk of hypokalaemia and recommendations for the monitoring of plasma potassium are detailed in section 4.4 of the SmPC. - Concomitant uses which could increase the risk of hypokalaemia and recommendations concerning plasma potassium monitoring are detailed in section 4.5 of the SmPC.

	- According to section 2 of the PIL, product must not be used in patients with low plasma potassium levels and the amount of potassium in blood may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Hyperkalaemia (including increased risk of hyperkalaemia when combining RAS agents)	
Evidence for linking the risk to the medicine	Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Hyperkalaemia reversible on discontinuation is listed with a frequency uncommon for perindopril mono-component of perindopril/ indapamide/ amlodipine FDC.
Risk factors and risk groups	Risk groups/factors for the development of hyperkalaemia include: - patients with renal insufficiency, worsening of renal function, - age (> 70 years), - diabetes mellitus, - intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, - concomitant use of potassium-sparing diuretics (e.g., spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium-containing salt substitutes; particularly in patients with impaired renal function (may lead to a significant increase in serum potassium), - patients taking other drugs associated with increases in serum potassium (e.g. heparin, co-trimoxazole also known as trimethoprim/sulfamethoxazole, aliskiren, other ACE inhibitors, angiotensin-II antagonists, acetylsalicylic acid ≥ 3 g/day, COX-2 inhibitors and non-selective NSAIDs, immunosuppressant agents such as ciclosporin or tacrolimus), - concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren (dual blockade of the renin-angiotensin-aldosterone system (RAAS).

Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A warning in section 4.4 of the SmPC states that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hyperkalaemia. - Concomitant uses which could increase the risk of hyperkalaemia and recommendations concerning the monitoring of serum potassium are detailed in section 4.5 of the SmPC. - There is a warning concerning the use of salt substitutes which contain potassium and medicines which should be avoided are detailed in section 2 of the PIL. The amount of potassium in blood may be checked by the doctor. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Neutropenia/agranulocytosis/thrombocytopenia	
Evidence for linking the risk to the medicine	Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Neutropenia has been observed during treatment with perindopril (very rare). Agranulocytosis has been observed during treatment with perindopril and indapamide (very rare). Thrombocytopenia has been observed during treatment with perindopril, amlodipine and indapamide with a frequency of very rare (SmPCs of mono-components).
Risk factors and risk groups	Patients with collagen vascular disease, immunosuppressant therapy, treatment with allopurinol or procainamide, or a combination of these complicating factors, especially if there is pre-existing impaired renal function.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8.

	- PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC stating that neutropenia / agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Foetotoxicity/use during 2nd and 3rd trimesters of pregnancy	
Evidence for linking the risk to the medicine	Exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (Perindopril SmPC) The prolonged exposure to thiazide during the third trimester of pregnancy can reduce maternal plasma volume as well as uteroplacental blood flow, which may cause a foeto-placental ischaemia and growth retardation (Indapamide SmPC).
Risk factors and risk groups	Women of childbearing potential. Pregnant women during the second or third trimester.
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication during the second and third trimester of pregnancy, is stated in sections 4.3 and 4.6 of the SmPC. - A warning concerning pregnancy is stated in section 4.4 of the SmPC. - In addition in section 4.6 of the SmPC is stated that exposure to ACE inhibitor therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension,

	hyperkalaemia). It is also stated that prolonged exposure to thiazide may cause a feto-placental ischemia and growth retardation. - According to section 2 of the PIL, product must not be used in patients who are more than 3 months pregnant. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Angioedema	
Evidence for linking the risk to the medicine	Angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and / or larynx has been reported rarely in patients treated with ACE inhibitors, including perindopril. This may occur at any time during therapy. Angioedema associated with laryngeal oedema may be fatal. Intestinal angioedema has been reported rarely in patients treated with ACE inhibitors. These patients presented with abdominal pain (with or without nausea or vomiting); in some cases there was no prior facial angioedema and C-1 esterase levels were normal.
Risk factors and risk groups	Known risk groups/risk factors include: - patients with a history of angioedema unrelated to ACE inhibitor therapy, - black patients (black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-blacks), - concomitant use with estramustine, gliptins ((linagliptine, saxagliptine, sitagliptine, vildagliptine), mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus), racecadotril, sacubitril/ valsartan.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk:

	- A contraindication in patients with hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, to other sulfonamides or to any of the excipients is stated in section 4.3 of the SmPC. - A contraindication in patients with history of angioedema associated with previous ACE inhibitor therapy is stated in section 4.3 of the SmPC. - A contraindication in patients with hereditary/idiopathic angioedema is stated in section 4.3 of the SmPC. - A contraindication in case of concomitant use with sacubitril/valsartan is stated in section 4.3 of the SmPC. - In addition there is a warning in section 4.4 of the SmPC stating that ACE inhibitors may cause angioedema of the face, extremities, lips, mucous membranes, tongue, glottis and / or larynx as well as intestinal angioedema. - Concomitant uses which could increase the risk of angioedema are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients who have experienced symptoms such as wheezing, swelling of the face, tongue or throat, intense itching or severe skin rashes with previous ACE inhibitor treatment or if you or a member of your family have had these symptoms in any other circumstances (a condition called angioedema). In this section is also stated that in case of swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing treatment must be stopped immediately. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Anaphylactoid reactions	
Evidence for linking the risk to the medicine	There have been isolated reports of patients experiencing sustained, life-threatening anaphylactoid reactions while receiving ACE inhibitors during desensitisation treatment with hymenoptera (bees, wasps) venom. Rarely, patients receiving ACE inhibitors during low density lipoprotein (LDL)-apheresis with dextran sulphate have experienced life-threatening anaphylactoid reactions. These reactions were avoided by temporarily withholding ACE-inhibitor therapy prior to each apheresis. Anaphylactoid reactions have been reported in patients dialysed with high-flux membranes (e.g., AN 69®) and treated concomitantly with an ACE inhibitor (Perindopril SmPC).
Risk factors and risk groups	Allergic patients treated with desensitisation, patients undergoing venom immunotherapy, patients undergoing low density lipoprotein (LDL)-apheresis, haemodialysis patients dialysed with high-flux membranes (e.g., AN 69®).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypersensitivity to the active substances, to ACE inhibitors, to dihydropyridines derivatives, to other sulfonamides or to any of the excipients is stated in section 4.3 of the SmPC. - A contraindication in case of extracorporeal treatments leading to contact of blood with negatively charged surfaces is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning anaphylactoid reactions during desensitization. - Concomitant uses which could increase the risk of anaphylactoid reactions are detailed in section 4.5 of the SmPC.

	- According to section 2 of the PIL, product must not be used in patients who are receiving dialysis or any other type of blood filtration. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Photosensitivity	
Evidence for linking the risk to the medicine	Cases of photosensitivity reactions have been reported with thiazides and thiazide-related diuretics. Photosensitivity reaction has been observed with the treatment of perindopril (uncommon), amlodipine (very rare) and indapamide (not known) (SmPC §4.8).
Risk factors and risk groups	Risk factor is exposure to the sun or to artificial UVA. In vivo and in vitro studies have indicated that UV-B and UV-A radiation could have additive or even synergistic effects (Gómez-Bernal; 2014).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC concerning photosensitivity reactions which have been reported with thiazides and thiazide-related diuretics. - There is a warning in section 2 of the PIL, stating that patients have to talk to their doctor if they have had photosensitivity reactions. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Hepatitis (including hepatic encephalopathy fulminant hepatitis)	
Evidence for linking the risk to the medicine	Hepatitis and possibility of onset of hepatic encephalopathy in case of hepatic insufficiency are listed with a frequency 'not known' (Indapamide SmPC). Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up. Hepatitis either cytolitic or cholestatic is listed with a frequenc 'very rare' (Perindopril SmPC). Hepatitis, jaundice, hepatic enzyme increased mostly consistent with cholestasis have been observed during the treatment with amlodipine (very rare) (Amlodipine SmPC).
Risk factors and risk groups	Risk factors according to the Guidelines of American College of Gastroenterology (ACG) – Variables that may predispose individuals to idiosyncratic DILI (3 categories) (Chalasani; 2014): Host factors: - Age (probably because the elderly receive multiple drugs and have low tolerability), - Gender female, - Pregnancy, - Malnutrition, - Obesity, - Diabetes mellitus, - Co-morbidities including underlying liver disease, - Indications for therapy. Environmental factors: - Smoking, - Alcohol consumption, - Infection and inflammatory episodes. Drug-related factors: - Daily dose, - Metabolic profile, - Class effect and cross-sensitization, - Drug interaction and polypharmacy. Predisposing factors for the development of hepatic encephalopathy are alcohol consumption, high levels of ammonia, zinc and branched chain amino acids, the

	presence of esophageal varices, and minimal hepatic encephalopathy. Electrolyte abnormalities, bleeding into the gastrointestinal tract, infections, high protein diet, diuretics, and sedatives may stimulate the development of hepatic encephalopathy (Ciećko-Michalska; 2012).
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hepatic encephalopathy and severe hepatic impairment is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning hepatic impairment. - According to section 2 of the PIL, product must not be used in patients who have severe liver disease or suffer from a condition called hepatic encephalopathy. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Myocardial infarction	
Evidence for linking the risk to the medicine	Myocardial infarction (possibly secondary to excessive hypotension in high risk patients) has been observed during the treatment with perindopril (very rare) and amlodipine (very rare) (SmPCs of mono-components).
Risk factors and risk groups	Known cardiovascular risk factors and risk modifiers include advanced age, gender, physical activity, smoking (current and former), high risk diet, overweight (abdominal obesity), diabetes, hypertension, hyperlipidaemia, socio-economic status, family history of premature cardio-vascular disease. Clinical conditions affecting cardiovascular disease risk include chronic kidney disease, autoimmune diseases, obstructive sleep apnoea syndrome (Piepoli; 2016). Risk groups include patients with ischaemic heart or cerebrovascular disease presenting risk factors for hypotension (see section SVII.3.1), patients with congestive heart failure, severe hypertension (including

	forms of hypertrophic obstructive cardiomyopathy), and severe aortic valve stenosis, patients with other cardiac valvular pathologies and low cardiac output states associated with a decreased mean aortic pressure, which is the prime component of coronary perfusion pressure.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with haemodynamically unstable heart failure after acute myocardial infarction is stated in section 4.3 of the SmPC. - There is a warning in section 4.4 of the SmPC concerning the risk of myocardial infarction which be leaded by an excessive fall in blood pressure. - According to section 2 of the PIL, product must not be used in patients who are suspected of having untreated decompensated heart failure and suffer from heart failure after a heart attack. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Arrhythmia	
Evidence for linking the risk to the medicine	Arrhythmia has been observed during the treatment with perindopril and indapamide (very rare); arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) has been observed during the treatment with amlodipine (uncommon). Electrocardiogram QT prolonged and torsade de pointes has been observed with indapamide (not known) (SmPCs of mono-components).

Risk factors and risk groups	Known risk factors of arrhythmia include structural heart disease: coronary heart disease, valvular disease, cardiomyopathy, heart failure, prior heart surgery, congenital heart disease, hypertension, left ventricular hypertrophy, thyroid hyper- or hypofunction, diabetes, obstructive sleep apnoea, electrolyte disorders, use of caffeine or other stimulants. Risk factors for ECG QT prolonged (Barnay; 2006); (Letsas; 2009) include: - Advanced age (> 60 years), - Female gender, - Bradycardia with sinus node dysfunction or atrioventricular block, - Electrolytes abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), - Cardiac diseases such as ischemia, myocarditis, dilated or hypertrophiccardiomyopathy, - Severe nutritional disorders (anorexia nervosa, cachexia, celiac disease), - Metabolic processing of pharmacological agents by cytochrome P450, - Other treatment known to induce QT prolonged. Risk factors for Torsade de pointes include (Gupta; 2007): - Female gender, - Structural heart disease: myocardial infarction, heart failure, valvular disease or cardiomyopathy, - Hypokalaemia, - Multiple QT prolonging drugs or agents interfering with their metabolism, - Prolonged baseline QT (drugs or agenFamily history of congenital long QT syndrome, - Prior drug-induced torsade de pointes, - Bradycardia, - Atrioventricular block.
Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: - A contraindication in patients with hypokalaemia is stated in section 4.3 of the SmPC.

	- Precautions for use concerning the risks of arrhythmias and recommendations for serum potassium monitoring are detailed in section 4.4 of the SmPC. - Concomitant uses which could increase the risk of arrhythmias and recommendations concerning the monitoring of serum potassium are detailed in section 4.5 of the SmPC. - According to section 2 of the PIL, product must not be used in patients with low plasma potassium levels and the amount of potassium in blood may be checked by the doctor. Product must not be used in patients taking non antiarrhythmic medicines causing life-threatening irregular beat. Patients have to talk to their doctor if they have any heart rhythm problems. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important identified risk: Pancreatitis	
Evidence for linking the risk to the medicine	Pancreatitis has been observed during the treatment with perindopril, indapamide, amolodipine (very rare) (SmPCs of mono-components).
Risk factors and risk groups	Risk groups/risk factors include: - Biliary tract disease, - Alcohol use, - Endoscopic retrograde cholangiopancreatography, - Abdominal trauma, - Developmental abnormalities of the pancreas (annular pancreas, pancreas divisum, sphincter of Oddi dysfunction), - Hypercalcemia (excessive vitamin D therapy, hyperparathyroidism, total parenteral nutrition), - Hypertriglyceridemia, - Tumors of pancreas, - Autoimmune disorders, - Type 2 diabetes, - Obesity (abdominal adiposity): the association is more important in patients with a waist circumference > 105 cm than in patients with a BMI > 30 kg.m2, - Smocking (Frossard; 2008); (Sadr-Azodi; 2012); (Sadr-Azodi; 2013); (Noel; 2009); (Girman; 2010).

Risk minimisation measures	Routine risk communication: - SmPC section 4.8. - PIL section 4. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important potential risk: Use during first trimester of pregnancy	
Evidence for linking the risk to the medicine	This risk is related to perindopril mono-component of the combination. Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded.
Risk factors and risk groups	Women of childbearing potential, pregnant women during the first trimester.
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a warning in section 4.4 of the SmPC stating that when pregnancy is diagnosed, treatment with ACE inhibitors should be stopped immediately. In addition, in section 4.6 it is stated that given the effects of the individual components in this combination product on pregnancy and lactation, bisoprolol/perindopril/amlodipine is not recommended during the first trimester of pregnancy. - According to section 2 of the PIL, patients should inform their doctors if they think they are (or might become) pregnant as product is not recommended in the early pregnancy. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Important potential risk: Pulmonary oedema in patients with heart failure	
Evidence for linking the risk to the medicine	In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group.
Risk factors and risk groups	Patients with heart failure, especially severe heart failure (NYHA III and IV).
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - According to section 2 of the PIL, product must not be used in patients who are suspected of having untreated decompensated heart failure and suffer from heart failure after a heart attack. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

Missing information: Children and adolescent	
Risk minimisation measures	Routine risk communication: - None Routine risk minimisation activities recommending specific clinical measures to address the risk: - There is a mention in section 4.2 of the SmPC stating that the safety and efficacy of product in children and adolescents have not been established. - In addition, there is a mention in section 5.1 of the SmPC stating that no data are available in children. - According to section 2 of the PIL, the use of product is not recommended in children and adolescents. - According to section 5 of the PIL, this medicine has to be kept out of the sight and reach of children. Other routine risk minimisation measures beyond the Product Information: Legal status: Restricted medical prescription medicine.

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 Viacorlix.

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

There are no studies required for Viacorlix.