Part VI Summary of the risk management plan

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions, including angioedema • Hyperkalaemia • Hypotension • Foetotoxicity when used in 2nd and 3rd trimester of pregnancy • Renal impairment – especially in patients with renal artery stenosis, pre-existing renal impairment, heart failure, post-myocardial infarction, dual blockade of RAAS • Pulmonary oedema – in patients with pre-existing heart failure NYHA grades III and IV • Hepatic impairment • Drug interactions (e.g. CYP3A4 inhibitors, lithium)
Important potential risks	• Risk of teratogenicity during the first trimester of pregnancy • Extrapyramidal syndrome
Missing information	• Use in patients with severe renal impairment (including recent kidney transplantation) • Use in paediatric patients • Use during breastfeeding • Effect on fertility

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

No study planned.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypersensitivity reactions, including angioedema	Included in SPC section(s) • 4.3 Contraindications Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients • 4.4 Special warnings and precautions for use: <u>Angioedema</u> Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE inhibitors. Amlodipine/valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered. • 4.8 Undesirable effects: <u>Summary of the safety profile</u> The safety of amlodipine/valsartan has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse	NA

	reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis, influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush. Immune system disorders: Hypersensitivity Valsartan Not known: hypersensitivity including serum sickness. Skin and subcutaneous tissue disorders: Angioedema Very rare Leukocytopenia, thrombocytopenia, allergic reactions, hyperglycaemia, hypertonia, peripheral neuropathy, myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), vasculitis, pancreatitis, gastritis, gingival hyperplasia, hepatitis, jaundice, hepatic enzymes increased *, angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity. Valsartan • Not known Decrease in haemoglobin, decrease in haematocrit,	

	neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.	
Hyperkalaemia	Included in SPC section(s) • 4.4 Special warnings and precautions for use: Hyperkalaemia Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (heparin, etc.) should be undertaken with caution and with frequent monitoring of potassium levels. Dual blockade of the renin-angiotensin-aldosterone system (RAAS) There is evidence that the concomitant use of ACE-inhibitors, ARBs 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, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is	NA

	considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. Amlodipine/valsartan has not been studied in any patient population other than hypertension. • 4.5 Interaction with other medicinal products and other forms of interaction: Dantrolene (infusion) In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren Clinical trial data have shown that dual blockade of the RAAS through the	

	combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. • 4.6 Fertility, pregnancy and lactation Valsartan The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. 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. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have	

	an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to AIIRA 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). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension. • 4.8 Undesirable effects Investigations: Blood potassium increased Valsartan Not known Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of	

	serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.	
Hypotension	Included in SPC section(s) • 4.3 Contraindications: Severe hypotension • 4.4 Special warnings and precautions for use: Sodium- and/or volume-depleted patients Excessive hypotension was seen in 0.4 % of patients with uncomplicated hypertension treated with amlodipine/valsartan in placebo-controlled studies. In patients with an activated renin-angiotensin system (such as volume- and/or salt-depleted patients receiving high doses of diuretics) who are receiving angiotensin receptor blockers, symptomatic hypotension may occur. Correction of this condition prior to administration of amlodipine/valsartan or close medical supervision at the start of treatment is recommended. If hypotension occurs with amlodipine/valsartan, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood	NA

	pressure has been stabilised. Dual blockade of the renin-angiotensin-aldosterone system (RAAS) There is evidence that the concomitant use of ACE-inhibitors, ARBs 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, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. • 4.5 Interaction with other medicinal products and other forms of interaction: Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency	

	of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. • 4.6 Fertility, pregnancy and lactation Valsartan The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. 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. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed,	

	treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to AIIRA 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). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension. • 4.8 Undesirable effects: Summary of the safety profile The safety of amlodipine/valsartan has been evaluated in five controlled clinical studies with 5,175 patients, 2,613 of whom received valsartan in combination with amlodipine. The following adverse reactions were found to be the most frequently occurring or the most significant or severe: nasopharyngitis,	

	influenza, hypersensitivity, headache, syncope, orthostatic hypotension, oedema, pitting oedema, facial oedema, oedema peripheral, fatigue, flushing, asthenia and hot flush. Vascular disorders: Hypotension Amlodipine/Valsartan: Hypotension rare Amlodipine: Hypotension uncommon Amlodipine Uncommon Insomnia, mood changes (including anxiety), depression, tremor, dysgeusia, syncope, hypoesthesia, visual disturbance (including diplopia), tinnitus, hypotension, dyspnoea, rhinitis, vomiting, dyspepsia, alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, exanthema, myalgia, muscle cramps, pain, micturition disorder, increased urinary frequency, impotence, gynaecomastia, chest pain, malaise, weight increase, weight decrease. • 4.9 Overdose: Symptoms: There is no experience of overdose with amlodipine/valsartan. The major symptom of overdose with valsartan is possibly pronounced hypotension with	

	dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. Treatment: If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to amlodipine/valsartan overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.	
Foetotoxicity when used in 2nd and 3rd trimester of	Included in SPC section(s) • 4.3 Contraindications:	NA

pregnancy	Second and third trimesters of pregnancy • 4.4 Special warnings and precautions for use: <u>Pregnancy</u> Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. • 4.6 Fertility, pregnancy and lactation: <u>Pregnancy:</u> <u>Amlodipine</u> The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses. Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. <u>Valsartan</u> The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during	

		the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. 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. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to AIIRA 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). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension	
Renal impairment – especially in patients with renal artery stenosis, pre-existing renal impairment, heart failure, post-myocardial infarction, dual blockade of RAAS	Included in SPC section(s) • 4.3 Contraindications: The concomitant use of amlodipine/valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) • 4.4 Special warnings and precautions for use: <u>Renal impairment</u> No dosage adjustment of amlodipine/valsartan is required for patients with mild to moderate renal impairment (GFR > 30 ml/min/1.73 m2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment. <u>Dual blockade of the renin-angiotensin-aldosterone system (RAAS)</u> There is evidence that the concomitant use of ACE-inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function	NA

	(including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy. Amlodipine/valsartan has not been studied in any patient population other than hypertension. • 4.5 Interaction with other medicinal products and other forms of interaction: <u>Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren</u> Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.	
Pulmonary oedema – in	Included in SPC section(s)	NA

patients with pre-existing heart failure NYHA grades III and IV	• 4.4 Special warnings and precautions for use: Heart failure/post-myocardial infarction As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as	

	compared to placebo. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.	
Hepatic impairment	Included in SPC section(s) • 4.2 Posology and method of administration: <u>Hepatic impairment</u> Amlodipine/valsartan is contraindicated in patients with severe hepatic impairment (. Caution should be exercised when administering amlodipine/valsartan to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to amlodipine or amlodipine/valsartan, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used. • 4.3 Contraindications: Severe hepatic	NA

	impairment, biliary cirrhosis or cholestasis. • 4.4 Special warnings and precautions for use: <u>Hepatic impairment</u> Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Particular caution should be exercised when administering amlodipine/valsartan to patients with mild to moderate hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.	
Drug interactions (e.g. CYP3A4 inhibitors, lithium)	Included in SPC section(s) • 4.5 Interaction with other medicinal products and other forms of interaction **Interactions common to the combination** No drug-drug interaction studies have been performed with amlodipine/valsartan and other medicinal products. **To be taken into account with concomitant use** *Other antihypertensive agents* Commonly used antihypertensive agents (e.g. alpha blockers,	NA

	diuretics) and other medicinal products which may cause hypotensive adverse effects (e.g. tricyclic antidepressants, alpha blockers for treatment of benign prostate hyperplasia) may increase the antihypertensive effect of the combination. **Interactions linked to amlodipine** **Concomitant use not recommended** *Grapefruit or grapefruit juice* Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects. ***Caution required with concomitant use*** *CYP3A4 inhibitors* Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be	

	required. CYP3A4 inducers *(anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum)* There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g. rifampicin, Hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers. *Simvastatin* Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine. *Dantrolene (infusion)* In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the	

	co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia. *To be taken into account with concomitant use* *Others* In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin. **Interactions linked to valsartan** *Concomitant use not recommended* *Lithium* Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, including valsartan. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with amlodipine/valsartan. *Potassium-sparing diuretics, potassium supplements, salt substitutes containing*	

	potassium and other substances that may increase potassium levels If a medicinal product that affects potassium levels is to be prescribed in combination with valsartan, monitoring of potassium plasma levels is advised. *<u>Caution required with concomitant use</u>* Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day), and non-selective NSAIDs When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient. *Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)* The results of an in vitro study with human liver	

	tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan. *Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren* Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. *Others* In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.	
Important potential risks		
Risk of teratogenicity during the first trimester of pregnancy	Included in SPC section(s) • 4.6 Fertility, pregnancy and lactation:	NA

	Pregnancy Valsartan The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. 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. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started. Exposure to AIIRA 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). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension.	
Extrapyramidal syndrome	Included in SPC section(s) • 4.8 Undesirable effects: <u>Nervous system disorders:</u> <u>Amlodipine:</u> Extrapyramidal syndrome not known **<u>Additional information on the individual components:</u>** *<u>Amlodpine:</u>* Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with amlodipine/valsartan as well, even if not observed in clinical trials or during the post-marketing period. Exceptional cases of extrapyramidal syndrome have been reported.	NA
Missing information		

Use in patients with severe renal impairment (including recent kidney transplantation)	Included in SPC section(s) • 4.2 Posology and method of administration: Renal impairment There are no available clinical data in severely renally impaired patients. No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. • 4.3 Contraindications: Severe renal impairment (glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2) and patients undergoing dialysis. The concomitant use of amlodipine/valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2). • 4.4 Special warnings and precautions for use: **Kidney transplantation** To date there is no experience of the safe use of amlodipine/valsartan in patients who have had a recent kidney transplantation. Renal impairment No dosage adjustment of amlodipine/valsartan is required for patients with mild to moderate renal impairment (GFR > 30 ml/min/1.73 m2). Monitoring of potassium	NA

	levels and creatinine is advised in moderate renal impairment. • 4.5 Interaction with other medicinal products and other forms of interaction: <u>Caution required with concomitant use</u> <u>Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day), and non-selective NSAIDs</u> When angiotensin II antagonists are administered simultaneously with NSAIDs attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient. • 4.6 Fertility, pregnancy and lactation: <u>Pregnancy</u> <u>Valsartan</u> Exposure to AIIRA 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). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension. • 4.8 Undesirable effects: Renal and urinary disorders: Renal failure and impairment	
Use in paediatric patients	Included in SPC section(s) • 4.2 Posology and method of administration: **Paediatric population** The safety and efficacy of amlodipine/valsartan in children aged below 18 years have not been established. No data are available.	NA
Use during breastfeeding	Included in SPC section(s) • 4.6 Fertility, pregnancy and lactation: <u>Breastfeeding</u> No information is available regarding the use of amlodipine/valsartan during breastfeeding, therefore amlodipine/valsartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are	NA

	preferable, especially while nursing a newborn or preterm infant.	
Effect on fertility	Included in SPC section(s) • 4.6 Fertility, pregnancy and lactation: Fertility There are no clinical studies on fertility with amlodipine/valsartan. *Valsartan* Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). *Amlodipine* Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility	NA

Amlodipine besilate/Valsartan was first approved in 2007. A well-established safety profile based on more than six years of post-authorisation experience with the originator product exists.

STADA Arzneimittel AG has an adequate Pharmacovigilance System in place.

All identified risks and missing information are sufficiently covered in the respective sections of the SPC. Therefore, no additional pharmacovigilance and risk minimisation activities are deemed necessary.
Currently available data on important potential risks do not support the need for additional pharmacovigilance and risk minimisation measures.