SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : **AMADAY PL 10/8** (Amlodipine 10 mg and Perindopril Erbumine 8 mg Tablets) **AMADAY PL 5/8** (Amlodipine 5 mg and Perindopril Erbumine 8 mg Tablets) **AMADAY PL 10/4** (Amlodipine 10 mg and Perindopril Erbumine 4 mg Tablets) **AMADAY PL 5/4** (Amlodipine 5 mg and Perindopril Erbumine 4 mg Tablets)
	1.2 Strength : **AMADAY PL 10/8** (Amlodipine 10 mg and Perindopril Erbumine 8 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 10 mg Perindopril Erbumine BP 8 mg **AMADAY PL 5/8** (Amlodipine 5 mg and Perindopril Erbumine 8 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 5 mg Perindopril Erbumine BP 8 mg Colour: Iron Oxide Red **AMADAY PL 10/4** (Amlodipine 10 mg and Perindopril Erbumine 4 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 10 mg Perindopril Erbumine BP 4 mg Colour: Iron Oxide Yellow **AMADAY PL 5/4** (Amlodipine 5 mg and Perindopril Erbumine 4 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 5 mg Perindopril Erbumine BP 4 mg
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **AMADAY PL 10/8** (Amlodipine 10 mg and Perindopril Erbumine 8 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 10 mg Perindopril Erbumine BP 8 mg **AMADAY PL 5/8** (Amlodipine 5 mg and Perindopril Erbumine 8 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 5 mg Perindopril Erbumine BP 8 mg Colour: Iron Oxide Red **AMADAY PL 10/4** (Amlodipine 10 mg and Perindopril Erbumine 4 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 10 mg Perindopril Erbumine BP 4 mg Colour: Iron Oxide Yellow

	AMADAY PL 5/4 (Amlodipine 5 mg and Perindopril Erbumine 4 mg Tablets) Each uncoated tablet contains: Amlodipine Besilate BP equivalent to Amlodipine 5 mg Perindopril Erbumine BP 4 mg For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	AMADAY PL 10/8 (Amlodipine 10 mg and Perindopril Erbumine 8 mg Tablets) White to off-white coloured, circular, biconvex, uncoated tablets, plain on both sides**.** **AMADAY PL 5/8** (Amlodipine 5 mg and Perindopril Erbumine 8 mg Tablets) Pink to light pink coloured, mottled, circular, biconvex, uncoated tablets, plain on both sides. **AMADAY PL 10/4** (Amlodipine 10 mg and Perindopril Erbumine 4 mg Tablets) Light yellow to yellow coloured, circular, biconvex, uncoated tablets, plain on both sides. **AMADAY PL 5/4** (Amlodipine 5 mg and Perindopril Erbumine 4 mg Tablets) White to off-white coloured, circular, biconvex, uncoated tablets, plain on both sides.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Perindopril/Amlodipine is indicated as substitution therapy for treatment of essential hypertension and/or stable coronary artery disease, in patients already controlled with perindopril and amlodipine given concurrently at the same dose level.
	4.2 Posology and Method of administration: Oral route. One tablet per day as a single dose, preferably to be taken in the morning and before a meal. The fixed dose combination is not suitable for initial therapy. If the change of the dosage is needed, it should be carried out by individual titration of the free combination's ingredients. *Patients with renal impairment and elderly* Elimination of perindoprilat is decreased in the elderly and in patients with renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium. Perindopril/Amlodipine can be administered in patients with Clcr ≥ 60 ml/min, and is not suitable for patients with Clcr < 60 ml/min. In these patients, an individual dose titration with the mono-components is recommended. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. *Patients with hepatic impairment:* A dosage regimen for patients with hepatic impairment has not been established. Therefore, Perindopril/Amlodipine should be administered with caution. *Paediatric population* Perindopril/Amlodipine should not be used in children and adolescents as the efficacy and tolerability of perindopril alone or in combination with amlodipine, have not been established in children and adolescents.
	4.3 Contraindications: *Linked to perindopril*

	• Hypersensitivity to perindopril or to any other ACE inhibitor. • History of angioedema associated with previous ACE inhibitor therapy. • Hereditary or idiopathic angioedema. • Second and third trimesters of pregnancy. *Linked to amlodipine* • Severe hypotension, • Hypersensitivity to amlodipine or to any other dihydropyridines, • Shock, including cardiogenic shock, • Obstruction of the outflow-tract of the left ventricle (e.g. high grade aortic stenosis), • Haemodynamically unstable heart failure after acute myocardial infarction. *Linked to Perindopril/Amlodipine* All contraindications related to each mono-component, as listed above, should apply also to the fixed combination of Perindopril/Amlodipine. • Hypersensitivity to any of the excipients.
	4.4 Special warning and precautions for use: All warnings related to each mono-component, as listed below, should also apply also to the fixed combination of Perindopril/Amlodipine. ***Linked to perindopril*** *Special warnings* *Hypersensitivity/Angioedema:* 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. In such cases, Perindopril/Amlodipine should promptly be discontinued and appropriate monitoring should be initiated and continued until complete resolution of symptoms has occurred. In those instances where swelling was confined to the face and lips the condition generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal oedema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, emergency therapy should be administered promptly. This may include the administration of adrenaline and/or the maintenance of a patent airway. The patient should be under close medical supervision until complete and sustained resolution of symptoms has occurred. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. 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. The angioedema was diagnosed by procedures including abdominal CT scan, or ultrasound or at surgery and symptoms resolved after stopping the ACE inhibitor. Intestinal angioedema should be included in the differential diagnosis of patients on ACE inhibitors presenting with abdominal pain. *Anaphylactoid reactions during low-density lipoproteins (LDL) apheresis:* 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 during desensitisation:
Patients receiving ACE inhibitors during desensitisation treatment (e.g. hymenoptera venom) have experienced anaphylactoid reactions. In the same patients, these reactions have been avoided when the ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Neutropenia/Agranulocytosis/Thrombocytopenia/Anaemia:
Neutropenia/agranulocytosis, thrombocytopenia and anaemia have been reported in patients receiving ACE inhibitors. In patients with normal renal function and no other complicating factors, neutropenia occurs rarely. Perindopril should be used with extreme caution in 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. Some of these patients developed serious infections, which in a few instances did not respond to intensive antibiotic therapy. If perindopril is used in such patients, periodic monitoring of white blood cell counts is advised and patients should be instructed to report any sign of infection (e.g. sore throat, fever).

Pregnancy:
ACE inhibitors should not be initiated during pregnancy. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE- inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. 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 angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Precautions for use
Hypotension:
ACE inhibitors may cause a fall in blood pressure. Symptomatic hypotension is seen rarely in uncomplicated hypertensive patients and is more likely to occur in patients who have been volume depleted e.g. by diuretic therapy, dietary salt restriction, dialysis, diarrhoea or vomiting, or who have severe renin-dependent hypertension. In patients at high risk of symptomatic hypotension, blood pressure, renal function and serum potassium should be monitored closely during treatment with Perindopril/Amlodipine.
Similar considerations apply to patients with ischaemic heart or cerebrovascular disease in whom an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident. If hypotension occurs, the patient should be placed in the supine position and, if necessary, should receive an intravenous infusion of sodium chloride 9 mg/ml (0.9%) solution. A transient hypotensive response is not a contraindication to further

doses, which can be given usually without difficulty once the blood pressure has increased after volume expansion.

Aortic and mitral valve stenosis / hypertrophic cardiomyopathy:
As with other ACE inhibitors, perindopril should be given with caution to patients with mitral valve stenosis and obstruction in the outflow of the left ventricle such as aortic stenosis or hypertrophic cardiomyopathy.

Renal impairement:
In cases of renal impairment (creatinine clearance < 60 ml/min) an individual dose titration with the monocomponents is recommended.
Routine monitoring of potassium and creatinine are part of normal medical practice for patients with renal impairment.
In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, who have been treated with ACE inhibitors, increases in blood urea and serum creatinine, usually reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. If renovascular hypertension is also present there is an increased risk of severe hypotension and renal insufficiency. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when perindopril has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment.

Hepatic failure:
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.

Ethnic differences:
ACE inhibitors cause a higher rate of angioedema in black patients than in non-black patients. As with other ACE inhibitors, perindopril may be less effective in lowering blood pressure in black people than in non-blacks, possibly because of a higher prevalence of low-renin states in the black hypertensive population

Cough:
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Surgery/Anaesthesia:
In patients undergoing major surgery or during anaesthesia with agents that produce hypotension, Perindopril/Amlodipine may block angiotensin II formation secondary to compensatory renin release. The treatment should be discontinued one day prior to the surgery. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Hyperkalaemia:
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including perindopril. Risk factors for the development of hyperkalaemia include those with renal insufficiency, worsening of renal function, age (> 70 years), diabetes

	mellitus, intercurrent events, in particular dehydration, acute cardiac decompensation, metabolic acidosis, and concomitant use of potassium-sparing diuretics (e.g. spironolactone, eplerenone, triamterene, or amiloride), potassium supplements or potassium containing salt substitutes; or those patients taking other drugs associated with increases in serum potassium (e.g. heparin). The use of potassium supplements, potassium-sparing diuretics, or potassium-containing salt substitutes particularly in patients with impaired renal function may lead to a significant increase in serum potassium. Hyperkaelemia can cause serious, sometimes fatal arrhythmias. If concomitant use of perindopril and any of the above mentioned agents is deemed appropriate, they should be used with caution and with frequent monitoring of serum potassium. *Diabetic patients:* In diabetic patients treated with oral antidiabetic agents or insulin, glycaemic control should be closely monitored during the first month of treatment with an ACE inhibitor. *Linked to amlodipine:* *Precautions for use* Patients with impaired hepatic function: As with all calcium antagonists, half-life of amlodipine is prolonged in patients with impaired liver function. The drug should therefore be administered with caution in these patients and with a close monitoring of the hepatic enzymes. Patients with heart failure: Patients with cardiac failure should be treated with caution. In a long-term, placebo controlled study of amlodipine in patients with NYHA III and IV heart failure of nonischaemic 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. *Linked to Perindopril/Amlodipine* *Precautions for use* Interactions The concomitant use of Perindopril/Amlodipine with lithium, potassium-sparing diuretics or potassium supplements is not recommended.
	4.5 Interactions with other medicinal products and other forms of Interactions : ***Linked to perindopril*** *Concomitant use not recommended:* Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes: Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with perindopril. Potassium-sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements or potassium containing salt substitutes may lead to significant increases in serum potassium. Therefore, the combination of perindopril with the above-mentioned drugs is not recommended. If concomitant use is indicated because of demonstrated hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium. Lithium: Reversible increases in serum lithium concentrations and toxicity (severe neurotoxicity) have been reported during concurrent use of ACE inhibitors. The

combination of perindopril with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Estramustine:
Risk of increased adverse effects such as angioneurotic oedema (angioedema).

Concomitant use which requires special care:
Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid ≥ 3 g/day:
When ACE-inhibitors are administered simultaneously with non-steroidal anti-inflammatory drugs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
Concomitant use of ACE-inhibitors and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Antidiabetic agents (insulin, hypoglycaemic sulphonamides): The use of angiotensin converting enzyme inhibitors may increase the hypoglycaemic effect in diabetics receiving treatment with insulin or with hypoglycaemic sulphonamides. The onset of hypoglycaemic episodes is very rare (there is probably an improvement in glucose tolerance with a resulting reduction in insulin requirements).

Concomitant use to be taken into consideration:
Diuretics: Patients on diuretics, and especially those who are volume and/or salt depleted, may experience excessive reduction in blood pressure after initiation of therapy with an ACE inhibitor. The possibility of hypotensive effects can be reduced by discontinuation of the diuretic, by increasing volume or salt intake prior to initiating therapy with low and progressive doses of perindopril.

Sympathomimetics:
Sympathomimetics may reduce the antihypertensive effects of ACE inhibitors.

Gold:
Nitritoid reactions (symptoms include facial flushing, nausea, vomiting and hypotension) have been reported rarely in patients on therapy with injectable gold (sodium aurothiomalate) and concomitant ACE inhibitor therapy including perindopril.

Linked to amlodipine
Concomitant use which requires special care:
CYP3A4 inhibitors:
With concomitant use with the CYP3A4 inhibitor erythromycin in young patients and diltiazem in elderly patients respectively the plasma concentration of amlodipine increased by 22% and 50 % respectively. However, the clinical relevance of this finding is uncertain. It cannot be ruled out that strong inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors. However, no adverse events attributable to such interaction have been reported.

	CYP3A4 inducers (rifampicin, Hypericum perforatum, anticonvulsant agents i.e carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone): The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine due to an increase of the hepatic metabolism of amlodipine by these inducers. Amlodipine should be used with caution together with CYP3A4 inducers and posology of amlodipine could be adapted if needed. *Concomitant use to be taken into consideration:* Beta-blockers used in heart failure (bisoprolol, carvedilol, metoprolol): Risk of hypotension, heart weakness in patients with cardiac heart failure, be it latent or uncontrolled (addition of negative inotropic effect). Furthermore, the beta-blocker may minimize the sympathic reflex in case of excessive heamodynamic repercussion. *Others combinations:* In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, digoxin, warfarin, atorvastatin, sildenafil, anti-acid medicines (aluminium hydroxide gel, magnesium hydroxide, simeticone), cimetidine, nonsteroidal antiinflammatory medicines, antibiotics and oral hypoglycaemic medicines. Indeed, specific studies conducted with some drugs have shown no influence on amlodipine: • Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine. • when sildenafil and amlodipine were used in combination, each one independently exerted its own blood pressure lowering effect. • grapefruit juice: co-administration of 240 ml of grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. Moreover, specific studies conducted with some drugs have shown that amlodipine has no influence on their pharmacokinetics parameters: • atorvastatin: co-administration of multiple doses of 10 mg amlodipine with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetics parameters of atorvastatin. • digoxin: co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. • warfarin: in heathy male volunteers, the co-administration of amlodipine did not significantly alter the effect of warfarin on prothrombin response time. Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time. • ciclosporin: Pharmacokinetic studies with ciclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of ciclosporin. *Concomitant use which requires special care:* Baclofen. Potentiation of antihypertensive effect. Monitoring of blood pressure and renal function, and dose adjustment of the antihypertensive if necessary. *Concomitant use to be taken into consideration:* • Antihypertensive agents (such as beta-blockers) and vasodilators: • Concomitant use of these agents may increase the hypotensive effects of perindopril and amlodipine. • Concomitant use with nitroglycerine and other nitrates or other vasodilators, may further reduce blood pressure and therefore should be considered with caution.

	• Corticosteroids, tetracosactide: reduction in antihypertensive effect (salt and water retention due to corticosteroids). • Alpha-blockers (prazosin, alfuzosin, doxazosin, tamsulosin, terazosin): increased antihypertensive effect and increased risk of orthostatic hypotension. • Amifostine: may potentiate the antihypertensive effect of amlodipine. • Tricyclic antidepressants/antipsychotics/anaesthetics: increased antihypertensive effect and increased risk of orthostatic hypotension.
	4.6 Pregnancy and Lactation: Given the effects of the individual components in this combination product on pregnancy and lactation: Perindopril/Amlodipine is not recommended during the first trimester of pregnancy. Perindopril/Amlodipine is contraindicated during the second and third trimesters of pregnancy. Perindopril/Amlodipine is not recommended during lactation. A decision should therefore be made whether to discontinue nursing or to discontinue Perindopril/Amlodipine taking into account the importance of this therapy for the mother. **Pregnancy:** ***Linked to perindopril*** The use of ACE inhibitors is not recommended during the first trimester of pregnancy. The use of ACE inhibitors is contraindicated during the second and third trimester 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. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started. 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). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken ACE inhibitors should be closely observed for hypotension. ***Linked to amlodipine*** The safety of amlodipine in human pregnancy has not been established. Data on a limited number of exposed pregnancies do not indicate that amlodipine or other calcium receptor antagonists have a harmful effect on the health of the fetus. However, there may be a risk of prolonged delivery. 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 fetus. **Lactation:** ***Linked to perindopril*** Because no information is available regarding the use of perindopril during breastfeeding, Perindopril/Amlodipine is not recommended and alternative treatments with better

established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Linked to amlodipine

It is not known whether amlodipine is excreted in breast milk. Similar calcium channel blockers of the dihydropyridine type are excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

4.7 Effects on ability to drive and use machine:
No studies on the effects of Perindopril/Amlodipine on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable Effects:
The following undesirable effects have been observed during treatment with perindopril or amlodipine given separately and ranked under the MedDRA classification by body system and under the following frequency:
• Very common (≥1/10)
• Common (≥1/100 to <1/10)
• Uncommon (≥1/1,000 to <1/100)
• Rare (≥1/10,000 to <1/1,000)
•Very rare (<1/10,000)
• Not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Undesirable Effects**	**Frequency**	
		Amlodipine	**Perindopril**
Blood and lymphatic system disorders	Leucopenia/neutropenia	Very rare	Very rare
	Agranulocytosis or pancytopenia		Very rare
	Thrombocytopenia	Very rare	Very rare
	Haemolytic anaemia in patients with a congenital deficiency of G-6PDH	-	Very rare
	Decrease in haemoglobin and haematocrit	-	Very rare
Immune system disorders	Allergic reaction: Urticaria	Very rare	Uncommon
Metabolism and nutrition disorders	Hyperglycaemia	Very rare	-
	Weight gain	Uncommon	-
	Weight decrease	Uncommon	-
	Hypoglycaemia	-	Not known

	Psychiatric disorders	Insomnia	Uncommon	-
		Mood changes	Uncommon	Uncommon
		Sleep disturbances	-	Uncommon
	Nervous system disorders	Somnolence	Common	-
		Dizziness	Common	Common
		Headache	Common	Common
		Tremor	Uncommon	-
		Hypoesthaesia, Paresthaesia	Uncommon	-
			Uncommon	Common
		Hypertonia	Very rare	-
		Peripheral neuropathy	Very rare	-
		Vertigo	-	Common
		Confusion	-	Very rare
		Visual disturbances	Uncommon	Common
		Tinnitus	Uncommon	Common
		Palpitations	Common	-
		Syncope	Uncommon	-
		Angina pain	Rare	-
		Angina pectoris	-	Very rare
		Myocardial infarction, possibly secondary to excessive hypotensionin high risk patients	Very rare	Very rare
		Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	Very rare	Very rare
		Flushing	Common	-
		Hypotension (and effects related to hypotension)	Uncommon	Common
		Stroke possibly secondary to excessive hypotension in high-risk patients	-	Very rare
		Vasculitis	Very rare	Not known
		Dyspnoea	Uncommon	Common
		Rhinitis	Uncommon	Very rare
		Cough	Very rare	Common
		Bronchospasm	-	Uncommon

Eosinophilic pneumonia	-	Very rare
Gingival hyperplasia	Very rare	-
Abdominal pain, nausea	Common	Common
Vomiting	Uncommon	Common
Dyspepsia	Uncommon	Common
Altered bowel habits	Uncommon	-
Dry mouth	Uncommon	Uncommon
Dysgeusia	-	Common
Taste perversion	Uncommon	-
Diarrhoea, constipation	-	Common
Pancreatitis	Very rare	Very rare
Gastritis	Very rare	-
Hepatitis, cholestatic jaundice	Very rare	-
Hepatitis either cytolitic or cholestatic	-	Very rare
Quincke's oedema	Very rare	-
Angioedema of face, extremities, lips, mucous membranes, tongue, glottis and/or larynx	-	Uncommon
Erythema multiform	Very rare	Very rare
Alopecia	Uncommon	-
Purpura	Uncommon	-
Skin discoloration	Uncommon	-
Increased sweating	Uncommon	-
Sweating	-	Uncommon
Pruritus	Uncommon	Common
Rash	Uncommon	Common
Stevens-Johnson Syndrome	Very rare	-
Arthralgia, myalgia	Uncommon	-
Muscle cramps	Uncommon	Common
Back pain	Uncommon	-
Micturition disorder, nocturia, increased urinary frequency	Uncommon	-
Renal impairment	-	Uncommon

	Acute renal failure	-	Very rare
	Impotence	Uncommon	Uncommon
	Gynaecomastia	Uncommon	
	Oedema, peripheral oedema	Common	-
	Fatigue	Common	-
	Chest pain	Uncommon	-
	Asthenia	Uncommon	Common
	Pain	Uncommon	-
	Malaise	Uncommon	-
	Hepatic enzymes elevations: ALT, AST (mostly consistent with cholestasis)	Very rare	-
	Serum bilirubin and liver enzymes elevation	-	Rare
	Increases in blood urea and serum creatinine, hyperkalaemia	-	Not known

Additional information linked to amlodipine
Exceptional cases of extrapyramidal syndrome have been reported with calcium channel blockers.

4.9 Overdosage:
There is no information on overdose with Perindopril/Amlodipine in humans.

For amlodipine, experience with intentional overdose in humans is limited. Large overdosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. Any hypotension due to amlodipine overdosage calls for a monitoring in cardiologic intensive care unit. 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.

Amlodipine is not dialyzable.

For perindopril, limited data are available for overdose in humans. Symptoms associated with the overdose of ACE inhibitors may include hypotension, circulatory shock, electrolyte disturbances, renal failure, hyperventilation, tachycardia, palpitations, bradycardia, dizziness, anxiety, and cough.

The recommended treatment of overdose is intravenous infusion of normal saline solution. If hypotension occurs, the patient should be placed in the shock position. If available, treatment with angiotensin II infusion and/or intravenous catecholamines may also be considered. Perindopril can be removed from the systemic circulation by haemodialysis. Pacemaker therapy is indicated for treatment-resistant bradycardia. Vital signs, serum electrolytes and creatinine concentrations should be monitored continuously.

5.	**Pharmacological properties**
	Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, ACE inhibitors and calcium channel blockers, ATC code: C09BB04. **5.1 Pharmacodynamic Properties:** **Perindopril** Perindopril is an inhibitor of the enzyme that converts angiotensin I into angiotensin II (Angiotensin Converting Enzyme ACE). The converting enzyme, or kinase, is an exopeptidase that allows conversion of angiotensin I into the vasoconstrictor angiotensin II as well as causing the degradation of the vasodilator bradykinin into an inactive heptapeptide. Inhibition of ACE results in a reduction of angiotensin II in the plasma, which leads to increased plasma renin activity (by inhibition of the negative feedback of renin release) and reduced secretion of aldosterone. Since ACE inactivates bradykinin, inhibition of ACE also results in an increased activity of circulating and local kallikreinkinin systems (and thus also activation of the prostaglandin system). It is possible that this mechanism contributes to the blood pressure-lowering action of ACE inhibitors and is partially responsible for certain of their side effects (e.g. cough). Perindopril acts through its active metabolite, perindoprilat. The other metabolites show no inhibition of ACE activity in vitro. Hypertension: Perindopril is active in all grades of hypertension: mild, moderate, severe; a reduction in systolic and diastolic blood pressures in both supine and standing positions is observed. Perindopril reduces peripheral vascular resistance, leading to blood pressure reduction. As a consequence, peripheral blood flow increases, with no effect on heart rate. Renal blood flow increases as a rule, while the glomerular filtration rate (GFR) is usually unchanged. The antihypertensive activity is maximal between 4 and 6 hours after a single dose and is sustained for at least 24 hours: trough effects are about 87-100% of peak effects. The decrease in blood pressure occurs rapidly. In responding patients, normalisation is achieved within a month and persists without the occurrence of tachyphylaxis. Discontinuation of treatment does not lead to a rebound effect. Perindopril reduces left ventricular hypertrophy. In man, perindopril has been confirmed to demonstrate vasodilatory properties. It improves large artery elasticity and decreases the media: lumen ratio of small arteries. **Amlodipine** Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully understood but is determined by the following two actions: 1. Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

	2. The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardium in patients with Prinzmetal's angina attack. In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure (in both supine and standing positions) throughout the 24 hour interval. In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression. Amlodipine decreases both angina attack frequency and glyceryl trinitrate tablet consumption. Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.
	5.2 Pharmacokinetics Properties: The rate and extent of absorption of perindopril and amlodipine from Perindopril/Amlodipine are not significantly different, respectively, from the rate and extent of absorption of perindopril and amlodipine from individual tablet formulations. *Perindopril* After oral administration, the absorption of perindopril is rapid and the peak concentration is achieved within 1 hour. The plasma half-life of perindopril is equal to 1 hour. Perindopril is a prodrug. Twenty seven percent of the administered perindopril dose reaches the bloodstream as the active metabolite perindoprilat. In addition to active perindoprilat, perindopril yields five metabolites, all inactive. The peak plasma concentration of perindoprilat is achieved within 3 to 4 hours. As ingestion of food decreases conversion to perindoprilat, hence bioavailability, perindopril should be administered orally in a single daily dose in the morning before a meal. It has been demonstrated a linear relationship between the dose of perindopril and its plasma exposure. The volume of distribution is approximately 0.2 l/kg for unbound perindoprilat. Protein binding of perindoprilat to plasma proteins is 20%, principally to angiotensin converting enzyme, but is concentration dependent. Perindoprilat is eliminated in the urine and the terminal half-life of the unbound fraction is approximately 17 hours, resulting in steady-state within 4 days. Elimination of perindoprilat is decreased in the elderly, and also in patients with heart or renal failure. Therefore, the usual medical follow-up will include frequent monitoring of creatinine and potassium. Dialysis clearance of perindoprilat is equal to 70 ml/min. Perindopril kinetics are modified in patients with cirrhosis: hepatic clearance of the parent molecule is reduced by half. However, the quantity of perindoprilat formed is not reduced and therefore no dosage adjustment is required. *Amlodipine* After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. Its

	bioavailability is not influenced by food. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins. The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites. About 60% of the administered dose is excreted in the urine, 10% as unchanged amlodipine.
	5.3 Preclinical Safety data: ***Perindopril*** In the chronic oral toxicity studies (rats and monkeys), the target organ is the kidney, with reversible damage. No mutagenicity has been observed in in vitro or in vivo studies. Reproduction toxicology studies (rats, mice, rabbits and monkeys) showed no sign of embryotoxicity or teratogenicity. However, angiotensin converting enzyme inhibitors, as a class, have been shown to induce adverse effects on late fetal development, resulting in fetal death and congenital effects in rodents and rabbits: renal lesions and an increase in peri- and postnatal mortality have been observed. No carcinogenicity has been observed in long term studies in rats and mice. ***Amlodipine*** *Carcinogenesis, Mutagenesis, Impairment of Fertility* Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels. Reproductive studies have shown that calcium antagonists induce embryotoxic and/or teratogenic effects in several species, mainly as distal skeletal malformations. There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells. Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg. *Based on patient weight of 50 kg.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Microcrystalline Cellulose BP, Mannitol BP, Croscarmellose Sodium BP, Colloidal Silicon Dioxide USPNF and Magnesium Stearate BP. Ferric oxide USPNF in Amaday PL 5/8 and Yellow Oxide of Iron IH in Amaday PL 10/4
	6.2 Incompatibilities: Not applicable

	6.3 Shelf life: 24 months
	6.4 Special Precautions for storage: Store below 25°C. Protect from light and moisture.
	6.5 Nature and contents of container: 10 tablets in Alu-Alu blister. 3 such blisters are packed in a carton along with pack-insert
	6.6 Special precautions for disposal: Not applicable
7.	**Marketing Authorization Holder:** Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (West), Mumbai- 400 067, India **Manufacturing Site Address:** Ajanta Pharma Limited Mirza-Palashbari Road, Village Kokjhar, Kamrup (R), Guwahati, Assam – 781128.
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** May 10, 2021