SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : **Lastavin AM 5/160** (Amlodipine 5 mg and Valsartan 160 mg Tablets USP) **Lastavin AM 10/160** (Amlodipine 10 mg and Valsartan 160 mg Tablets USP)
	1.2 Strength : **Lastavin AM 5/160 (Amlodipine 5 mg and Valsartan 160 mg Tablets USP)** Each film coated tablet contains: Amlodipine Besylate USP Equivalent to Amlodipine……...5 mg Valsartan USP……160 mg Excipients…….q.s **Lastavin AM 10/160 (Amlodipine 10 mg and Valsartan 160 mg Tablets USP)** Each film coated tablet contains: Amlodipine Besylate USP Equivalent to Amlodipine……...10 mg Valsartan USP……160 mg Excipients…….q.s
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **Lastavin AM 5/160 (Amlodipine 5 mg and Valsartan 160 mg Tablets USP)** Each film coated tablet contains: Amlodipine Besylate USP Equivalent to Amlodipine……...5 mg Valsartan USP……160 mg Excipients…….q.s **Lastavin AM 10/160 (Amlodipine 10 mg and Valsartan 160 mg Tablets USP)** Each film coated tablet contains: Amlodipine Besylate USP Equivalent to Amlodipine……...10 mg Valsartan USP……160 mg Excipients…….q.s For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:**
	Film coated tablets
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: Treatment of essential hypertension. • Valsartan/ Amlodipine is indicated in adults whose blood pressure is not adequately

	controlled on amlodipine or valsartan monotherapy.
	4.2 Posology and Method of administration: Posology The recommended dose of Valsartan/ Amlodipine is one tablet per day. Valsartan/ Amlodipine 5 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5 mg or valsartan 160 mg alone. Valsartan/ Amlodipine 10 mg/160 mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10 mg or valsartan 160 mg alone or with Valsartan/ Amlodipine 5 mg/160 mg. Valsartan/ Amlodipine can be used with or without food. Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered. For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to Valsartan/ Amlodipine containing the same component doses. *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. *Hepatic impairment* Valsartan/ Amlodipine is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering Valsartan/ Amlodipine to patients with hepatic impairment or biliary obstructive disorders (see section 4.4). 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 Valsartan/ Amlodipine, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used. *Elderly (age 65 years or over)* In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or Valsartan/ Amlodipine, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used. *Paediatric population* The safety and efficacy of Valsartan/ Amlodipine in children aged below 18 years have not been established. No data are available. Method of administration Oral use. It is recommended to take Valsartan/ Amlodipine with some water.
	4.3 Contraindications: • Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients. • Severe hepatic impairment, biliary cirrhosis or cholestasis.

	• Concomitant use of Valsartan/ Amlodipine with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m^2) • Second and third trimesters of pregnancy. • Severe hypotension. • Shock (including cardiogenic shock). • Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis). • Haemodynamically unstable heart failure after acute myocardial infarction.
	4.4 Special warning and precautions for use: The safety and efficacy of amlodipine in hypertensive crisis have not been established. Pregnancy 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 (see sections 4.3 and 4.6). Sodium- and/or volume-depleted patients Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Valsartan/ Amlodipine 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 Valsartan/ Amlodipine or close medical supervision at the start of treatment is recommended. If hypotension occurs with Valsartan/ Amlodipine, 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 pressure has been stabilised. 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. Renal artery stenosis Valsartan/ Amlodipine should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients. Kidney transplantation To date there is no experience of the safe use of Valsartan/ Amlodipine in patients who have had a recent kidney transplantation. Hepatic impairment 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 Valsartan/ Amlodipine 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. Renal impairment No dosage adjustment of Valsartan/ Amlodipine is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m^2). Monitoring of potassium levels and creatinine is advised in moderate renal impairment. Primary hyperaldosteronism Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is affected by the primary disease. Angioedema 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. Valsartan/ Amlodipine should be discontinued immediately in patients who develop angioedema and should not be re-administered. 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. Aortic and mitral valve stenosis As with all other vasodilators, special caution is indicated in patients suffering from mitral stenosis or significant aortic stenosis that is not high grade. 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 (see sections 4.5 and 5.1). 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.

	Valsartan/ Amlodipine has not been studied in any patient population other than hypertension.
	4.5 Interactions with other medicinal products and other forms of Interactions : Interactions common to the combination No drug-drug interaction studies have been performed with Valsartan/ Amlodipine and other medicinal products. *To be taken into account with concomitant use* *Other antihypertensive agents* Commonly used antihypertensive agents (e.g. alpha blockers, 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)* Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum). *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 diurectic is also used, the risk of lithium toxicity may presumably be increased further with Valsartan/ Amlodipine. *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. *Caution required with concomitant use* *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, cyclosporine) 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, cyclosporine) 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, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.
	4.6 Pregnancy and Lactation: Pregnancy *Amlodipine* The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). 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. *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. Breast-feeding Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3–7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of Valsartan/ Amlodipine during breast-feeding, therefore Valsartan/ Amlodipine is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant. Fertility There are no clinical studies on fertility with Valsartan/ Amlodipine. *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/m^2 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.
	4.7 Effects on ability to drive and use machine: Patients taking Valsartan/ Amlodipine and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur. Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.
	4.8 Undesirable Effects: Summary of the safety profile

The safety of Valsartan/ Amlodipine 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.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention: 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).

MedDRA System organ class	**Adverse reactions**	**Frequency**		
		Valsartan/ Amlodipine	**Amlodipine**	**Valsartan**
Infections and infestations	Nasopharyngitis	Common	--	--
	Influenza	Common	--	--
Blood and lymphatic system disorders	Haemoglobin and haematocrit decreased	--	--	Not known
	Leukopenia	--	Very rare	--
	Neutropenia	--	--	Not known
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not known
Immune system disorders	Hypersensitivity	Rare	Very rare	Not known
Metabolism and nutrition disorders	Anorexia	Uncommon	--	--
	Hypercalcaemia	Uncommon	--	--
	Hyperglycaemia	--	Very rare	--
	Hyperlipidaemia	Uncommon	--	--
	Hyperuricaemia	Uncommon	--	--
	Hypokalaemia	Common	--	--
	Hyponatraemia	Uncommon	--	--
Psychiatric disorders	Depression	--	Uncommon	--
	Anxiety	Rare	--	--
	Insomnia/sleep disorders	--	Uncommon	--
	Mood swings	--	Uncommon	--
	Confusion	--	Rare	--

	Nervous system disorders	Coordination abnormal	Uncommon	--	--
		Dizziness	Uncommon	Common	--
		Dizziness postural	Uncommon	--	--
		Dysgeusia	--	Uncommon	--
		Extrapyramidal syndrome	--	Not known	--
		Headache	Common	Common	--
		Hypertonia	--	Very rare	--
		Paraesthesia	Uncommon	Uncommon	--
		Peripheral neuropathy, neuropathy	--	Very rare	--
		Somnolence	Uncommon	Common	--
		Syncope	--	Uncommon	--
		Tremor	--	Uncommon	--
		Hypoesthesia	--	Uncommon	--
	Eye disorders	Visual disturbance	Rare	Uncommon	--
		Visual impairment	Uncommon	Uncommon	--
	Ear and labyrinth disorders	Tinnitus	Rare	Uncommon	--
		Vertigo	Uncommon	--	Uncommon
	Cardiac disorders	Palpitations	Uncommon	Common	--
		Syncope	Rare	--	--
		Tachycardia	Uncommon	--	--
		Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	--	Very rare	--
		Myocardial infarction	--	Very rare	--
	Vascular disorders	Flushing	--	Common	--
		Hypotension	Rare	Uncommon	--
		Orthostatic hypotension	Uncommon	--	--
		Vasculitis	--	Very rare	Not known
	Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon
		Dyspnoea	--	Uncommon	--
		Pharyngolaryngeal pain	Uncommon	--	--
		Rhinitis	--	Uncommon	--

	Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon
		Change of bowel habit	--	Uncommon	--
		Constipation	Uncommon	--	--
		Diarrhoea	Uncommon	Uncommon	--
		Dry mouth	Uncommon	Uncommon	--
		Dyspepsia	--	Uncommon	--
		Gastritis	--	Very rare	--
		Gingival hyperplasia	--	Very rare	--
		Nausea	Uncommon	Common	--
		Pancreatitis	--	Very rare	--
		Vomiting	--	Uncommon	--
	Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare*	Not known
		Hepatitis	--	Very rare	--
		Intrahepatic cholestasis, jaundice	--	Very rare	--
	Skin and subcutaneous tissue disorders	Alopecia	--	Uncommon	--
		Angioedema	--	Very rare	Not known
		Dermatitis bullous	--	--	Not known
		Erythema	Uncommon	--	--
		Erythema multiforme	--	Very rare	--
		Exanthema	Rare	Uncommon	--
		Hyperhidrosis	Rare	Uncommon	--
		Photosensitivity reaction	--	Uncommon	--

		Pruritus	Rare	Uncommon	Not known
		Purpura	--	Uncommon	--
		Rash	Uncommon	Uncommon	Not known
		Skin discolouration	--	Uncommon	--
		Urticaria and other forms of rash	--	Very rare	--
		Exfoliative dermatitis	--	Very rare	--
		Stevens-Johnson syndrome	--	Very rare	--
		Quincke oedema	--	Very rare	--
		Toxic Epidermal Necrolysis	--	Not known	--
	Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--
		Back pain	Uncommon	Uncommon	--
		Joint swelling	Uncommon	--	--
		Muscle spasm	Rare	Uncommon	--
		Myalgia	--	Uncommon	Not known
		Ankle swelling	--	Common	--
		Sensation of heaviness	Rare	--	--
	Renal and urinary disorders	Blood creatinine increased	--	--	Not known
		Micturition disorder	--	Uncommon	--
		Nocturia	--	Uncommon	--
		Pollakiuria	Rare	Uncommon	--
		Polyuria	Rare	--	--
		Renal failure and impairment	--	--	Not known
	Reproductive system and breast disorders	Impotence	--	Uncommon	--
		Erectile dysfunction	Rare	--	--
		Gynaecomastia	--	Uncommon	--
	General disorders and administration site conditions	Asthenia	Common	Uncommon	--
		Discomfort, malaise	--	Uncommon	--
		Fatigue	Common	Common	Uncommon
		Facial oedema	Common	--	--
		Flushing, hot flush	Common	--	--
		Non cardiac chest pain	--	Uncommon	--

	Oedema	Common	Common	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
Investigations	Blood potassium increased	--	--	Not known
	Weight increase	--	Uncommon	--
	Weight decrease	--	Uncommon	--

* Mostly consistent with cholestasis

Additional information on the combination

Peripheral oedema, a recognised side effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone. In double-blind, controlled clinical trials, the incidence of peripheral oedema by dose was as follows:

% of patients who experienced peripheral oedema		**Valsartan (mg)**				
		0	40	80	160	320
Amlodipine (mg)	0	3.0	5.5	2.4	1.6	0.9
	2.5	8.0	2.3	5.4	2.4	3.9
	5	3.1	4.8	2.3	2.1	2.4
	10	10.3	NA	NA	9.0	9.5

The mean incidence of peripheral oedema evenly weighted across all doses was 5.1% with the amlodipine/valsartan combination.

Additional information on the individual components

Adverse reactions previously reported with one of the individual components (amlodipine or valsartan) may be potential adverse reactions with Valsartan/ Amlodipine as well, even if not observed in clinical trials or during the post-marketing period.

Amlodipine

Common Somnolence, dizziness, palpitations, abdominal pain, nausea, ankle swelling.

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.

Rare Confusion.

	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. *Not known* Toxic Epidermal Necrolysis * mostly consistent with cholestasis Exceptional cases of extrapyramidal syndrome have been reported. <u>*Valsartan*</u> *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.
	4.9 Overdosage: <u>Symptoms</u> There is no experience of overdose with Valsartan/ Amlodipine. 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. <u>Treatment</u> 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 Valsartan/ Amlodipine 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. Both valsartan and amlodipine are unlikely to be removed by haemodialysis.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: **Pharmacotherapeutic Group :** Amlodipine Besilate: Calcium Channel Blockers Valsartan: Angiotensin II Receptor Antagonist **ATC Code :** Amlodipine Besilate: C08CA01 Valsartan: C09CA03

	Valsartan/ Amlodipine combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. Amlodipine/Valsartan The combination of amlodipine and valsartan produces dose-related additive reduction in blood pressure across its therapeutic dose range. The antihypertensive effect of a single dose of the combination persisted for 24 hours. Amlodipine The amlodipine component of Valsartan/ Amlodipine inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Plasma concentrations correlate with effect in both young and elderly patients. In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria. As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans. Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. Valsartan Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT_1, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT_2, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

	Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($p < 0.05$) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%, respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced coughing, compared to 68.5% of those treated with an ACE inhibitor ($p < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate. In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4–6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2–4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.
	5.2 Pharmacokinetics Properties: <u>Linearity</u> Amlodipine and valsartan exhibit linear pharmacokinetics. <u>Amlodipine/Valsartan</u> Following oral administration of Valsartan/ Amlodipine, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Valsartan/ Amlodipine are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets. <u>Amlodipine</u> *Absorption:* After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion. *Distribution:* Volume of distribution is approximately 21 l/kg. *In vitro* studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins. *Biotransformation:* Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites. *Elimination:* Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7–8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine. <u>Valsartan</u> *Absorption:* Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food

	decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food. *Distribution:* The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin. *Biotransformation:* Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive. *Elimination:* Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.
	5.3 Preclinical Safety data: <u>Amlodipine/Valsartan</u> Adverse reactions observed in animal studies with possible clinical relevance were as follows: Histopathological signs of inflammation of the glandular stomach was seen in male rats at an exposure of about 1.9 (valsartan) and 2.6 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. At higher exposures, there were ulceration and erosion of the stomach mucosa in both females and males. Similar changes were also seen in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan). An increased incidence and severity of renal tubular basophilia/hyalinisation, dilation and casts, as well as interstitial lymphocyte inflammation and arteriolar medial hypertrophy were found at an exposure of 8–13 (valsartan) and 7–8 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160 mg valsartan). In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160 mg valsartan and 10 mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160 mg valsartan). There were only modest signs of maternal toxicity (moderate reduction of body weight) in this study. The no-observed-effect-level for developmental effects was observed at 3- (valsartan) and 4- (amlodipine) fold the clinical exposure (based on AUC). For the single compounds there was no evidence of mutagenicity, clastogenicity or carcinogenicity. <u>Amlodipine</u> <u>*Reproductive toxicology*</u> 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. *Impairment of fertility* 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/m^2 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. *Carcinogenesis, mutagenesis* 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/m^2 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. * Based on patient weight of 50 kg Valsartan Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised blood urea nitrogen, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients:

	Microcrystalline Cellulose, Yellow Oxide of Iron, Crospovidone , Colloidal Anhydrous Silica, Povidone, Sodium Starch Glycolate Type A, Magnesium Stearate, Instacoat EHP 250 A10R00390 Beige (Polyvinyl Alcohol, Glycerol Monostearate/Glyceryl Monostearate, Polysorbate 80, Diethyl Phthalate, Magnesium Stearate, Polyethylene Glycol, Modified Starch, Titanium Dioxide, Lake Sunset Yellow, Black Iron Oxide and Yellow Iron Oxide) for Amlodipine 5 mg and Valsartan 160 mg Tablets USP & Instacoat EHP 250 A10R00393 Brown (Polyvinyl Alcohol, Glycerol Monostearate/Glyceryl Monostearate, Polysorbate 80, Diethyl Phthalate, Magnesium Stearate, Polyethylene Glycol, Modified Starch, Titanium Dioxide, Red Iron Oxide and Black Iron Oxide) Amlodipine 10 mg and Valsartan 160 mg Tablets USP, and Purified water.
	6.2 Incompatibilities: Not Applicable
	6.3 Shelf life: 30 Months
	6.4 Special Precautions for storage: Store below 30°C.
	6.5 Nature and contents of container: Available in Alu-Alu blister of 10 tablets. Such 3 blisters of 10 tablets each along with package insert in a carton.
	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 Plot No. B-4/5/6, MIDC Paithan, Aurangabad 431148 Maharashtra State, India. e-mail: info@ajantapharma.com
8.	**Marketing Authorization Numbers:** Not applicable
9.	**Date of first registration /renewal of the registration:** Not Applicable
10.	**Date of revision of text:** Sep 06, 2021