SUMMARY OF PRODUCT CHARACTERISTICS

1.	**Name of the Medical Product**
	1.1 Product Name : Lastavin 80 (Valsartan Tablets USP 80 mg) Lastavin 160 (Valsartan Tablets USP 160 mg)
	1.2 Strength : **Lastavin 80 (Valsartan Tablets USP 80 mg)** Each film coated tablet contains: Valsartan USP…….80 mg **Lastavin 160 (Valsartan Tablets USP 160 mg)** Each film coated tablet contains: Valsartan USP…….160 mg
	1.3 Pharmaceutical Dosage Form : Tablet
2.	**Qualitative & Quantitative Composition:** **Lastavin 80 (Valsartan Tablets USP 80 mg)** Each film coated tablet contains: Valsartan USP…….80 mg **Lastavin 160 (Valsartan Tablets USP 160 mg)** Each film coated tablet contains: Valsartan USP…….160 mg 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: **Hypertension** • Treatment of essential hypertension in adults, and hypertension in children and adolescents 6 to 18 years of age. **Recent myocardial infarction** • Treatment of clinically stable adult patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours-10 days) myocardial infarction. **Heart failure** Treatment of adult patients with symptomatic heart failure when ACE-inhibitors are not tolerated or in beta-blocker intolerant patients as add-on therapy to ACE-inhibitors when mineralocorticoid receptor antagonists cannot be used.
	4.2 Posology and Method of administration:

	Hypertension The recommended starting dose of Valsartan is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg. Valsartan may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients. Recent myocardial infarction In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet. The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dosage reduction. Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended. Evaluation of post-myocardial infarction patients should always include assessment of renal function. Heart failure The recommended starting dose of Valsartan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done at intervals of at least two weeks to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses. Valsartan may be administered with other heart failure therapies. However, the triple combination of an ACE-inhibitor, valsartan and a beta-blocker or a potassium-sparing diuretic is not recommended. Evaluation of patients with heart failure should always include assessment of renal function. *Additional information on special populations* Elderly No dose adjustment is required in elderly patients. Renal impairment No dose adjustment is required for adult patients with a creatinine clearance >10 ml/min. Concomitant use of valsartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m^2).

Diabetes Mellitus

Concomitant use of valsartan with aliskiren is contraindicated in patients with diabetes mellitus.

Hepatic impairment

Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80 mg.

Paediatric population

Children and adolescents 6 to less than 18 years of age

For valsartan tablets, the initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response and tolerability. For maximum doses studied in clinical trials please refer to the table below.

Doses higher than those listed have not been studied and are therefore not recommended.

Weight	Maximum dose studied of tablet in clinical trials
≥18 kg to <35 kg	80 mg
≥35 kg to <80 kg	160 mg
≥80 kg to ≤160 kg	320 mg

For children already started on valsartan prior to the age of six years, please refer to the posology for valsartan oral solution (Children 1 to less than 6 years of age).

Children less than 6 years of age

For children aged 1 to 5 years and for those having difficulties in swallowing the tablet, valsartan oral solution is recommended. The safety and efficacy of valsartan in children below 1 year of age have not been established.

Switching from valsartan oral solution to valsartan tablets

If switching from valsartan oral solution to valsartan tablets is considered clinically essential, initially the same dose in milligrams should be given. Subsequently, frequent blood pressure monitoring should be performed taking into account potential under-dosing and the dose should be titrated further based on blood pressure response and tolerability.

Use in paediatric patients aged 6 to less than 18 years with renal impairment

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored.

Use in paediatric patients aged 6 to less than 18 years with hepatic impairment

As in adults, Valsartan is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment.

	The dose of valsartan should not exceed 80 mg in these patients. *Paediatric heart failure and recent myocardial infarction* Valsartan is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy. ***Method of administration*** Valsartan may be taken independently of a meal and should be administered with water.
	4.3 Contraindications: • Hypersensitivity to the active substance or to any of the excipients. • Severe hepatic impairment, biliary cirrhosis and cholestasis. • Second and third trimester of pregnancy. • The concomitant use of valsartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2).
	4.4 Special warning and precautions for use: ***Hyperkalaemia*** Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate. ***Impaired renal function*** There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dosage adjustment is required for adult patients with a creatinine clearance >10 ml/min. The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73m^2) ***Hepatic impairment*** In patients with mild to moderate hepatic impairment without cholestasis, Valsartan should be used with caution. ***Sodium and/or volume depleted patients*** In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose. ***Renal artery stenosis*** In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Valsartan has not been established.

Short-term administration of Valsartan to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation

There is currently no experience on the safe use of Valsartan in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with Valsartan as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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.

Recent myocardial infarction

The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies. Therefore, the combination of valsartan with an ACE inhibitor is not recommended. Caution should be observed when initiating therapy in post-myocardial infarction patients.

Evaluation of post-myocardial infarction patients should always include assessment of renal function. Use of Valsartan in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

Heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when [Product name] is used in combination with an ACE-inhibitor. In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and valsartan has not shown any clinical benefit. This combination apparently increases the risk for adverse events and is therefore not recommended. Triple combination of an ACE-inhibitor, a mineralocorticoid receptor

antagonist and valsartan is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function.

Use of Valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACE-inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Valsartan may be associated with impairment of the renal function**.**

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

History of 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 drugs including ACE inhibitors. Valsartan should be immediately discontinued in patients who develop angioedema, and valsartan should not be re-administered.

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.

Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2) is contraindicated.

Paediatric population

Impaired renal function

Use in paediatric patients with a creatinine clearance <30 ml/min and paediatric patients

	undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for paediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function. The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73m^2) <u>Impaired hepatic function</u> As in adults, Valsartan is contraindicated in paediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with Valsartan in paediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.
	4.5 Interactions with other medicinal products and other forms of Interactions : Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers 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. ***Dual blockade of the Renin-Angiotensin- System (RAS) with ARBs, ACEIs, or aliskiren:*** Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73m^2) is contraindicated. ***<u>Concomitant use not recommended</u>*** *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 with valsartan. If the combination proves necessary, careful monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further. *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 considered necessary 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. *Transporters* *In vitro* data indicates that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (e.g. rifampin, cyclosporine) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs. *Others* In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. *Paediatric population* In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.
	4.6 Pregnancy and Lactation: **Pregnancy:** The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated 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. Whilst there is no controlled epidemiological data on the risk with 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 anti-hypertensive 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. AIIRAs therapy exposure 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 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

Because no information is available regarding the use of valsartan during breastfeeding, Valsartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

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).

4.7 Effects on ability to drive and use machine:

No studies on the effects on the ability to drive 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:

In controlled clinical studies in adult patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse reactions are ranked by frequency, the most frequent first, 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness. For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a 'not known' frequency.

- Hypertension

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium, hyponatraemia
Ear and labyrinth system disorders	
Uncommon	Vertigo
Vascular disorders	

Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Dermatitis bullous, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinine
General disorders and administration site conditions	
Uncommon	Fatigue

Paediatric population

Hypertension

The antihypertensive effect of valsartan has been evaluated in two randomised, double-blind clinical studies (each followed by an extensive period or study) and one open-label study. These studies included 771 paediatric patients from 6 to less than 18 years of age with and without chronic kidney disease (CKD), of which 560 patients received valsartan. With the exception of isolated gastrointestinal disorders (such as abdominal pain, nausea, vomiting) and dizziness, no relevant differences in terms of type, frequency and severity of adverse reactions were identified between the safety profile for paediatric patients aged 6 to less than 18 years and that previously reported for adult patients.

A pooled analysis of 560 paediatric hypertensive patients (aged 6-17 years) receiving either valsartan monotherapy [n=483] or combination antihypertensive therapy including valsartan [n=77] was conducted. Of the 560 patients, 85 (15.2%) had CKD (baseline GFR <90 mL/min/1.73m2). Overall, 45 (8.0%) patients discontinued a study due to adverse events. Overall 111 (19.8%) patients experienced an adverse drug reaction (ADR), with headache (5.4%), dizziness (2.3%) and hyperkalaemia (2.3%) being the most frequent. In patients with CKD, the most frequent ADRs were hyperkalaemia (12.9%), headache (7.1%), blood creatinine increased (5.9%) and hypotension (4.7%). In patients without CKD, the most frequent ADRs were headache (5.1%) and dizziness (2.7%). ADRs were observed more frequently in patients receiving valsartan in combination with other antihypertensive medications than valsartan alone.

Neurocognitive and developmental assessment of paediatric patients aged 6 to 16 years of

age revealed no overall clinically relevant adverse impact after treatment with Valsartan for up to one year.
In a double-blind randomized study in 90 children aged 1 to 6 years, which was followed by a one-year open-label extension, two deaths and isolated cases of marked liver transaminases elevations were observed. These cases occurred in a population who had significant comorbidities. A causal relationship to Valsartan has not been established. In a second study in which 75 children aged 1 to 6 years were randomised, no significant liver transaminase elevations or death occurred with valsartan treatment.
Hyperkalaemia was more frequently observed in children and adolescents aged 6 to 18 years with underlying chronic kidney disease.
The safety profile seen in controlled-clinical studies in adult patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in adult patients with post-myocardial infarction and/or heart failure patients are listed below:
- **Post-myocardial infarction and/or heart failure (studied in adult patients only)**

Blood and lymphatic system disorders	
Not known	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Not known	Increase of serum potassium, hyponatraemia
Nervous system disorders	
Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, Diarrhoea
Hepato-biliary disorders	

	Not known	Elevation of liver function values
	Skin and subcutaneous tissue disorders	
	Uncommon	Angioedema
	Not known	Dermatitis bullous, Rash, Pruritus
	Musculoskeletal and connective tissue disorders	
	Not known	Myalgia
	Renal and urinary disorders	
	Common	Renal failure and impairment
	Uncommon	Acute renal failure, Elevation of serum creatinine
	Not known	Increase in Blood Urea Nitrogen
	General disorders and administration site conditions	
	Uncommon	Asthenia, Fatigue

4.9 Overdosage:

Symptoms

Overdose with Valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock.

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition is of prime importance.

If hypotension occurs, the patient should be placed in the supine position and blood volume correction should be undertaken.

Valsartan is unlikely to be removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic Group : The angiotensin II receptor blocker

ATC Code : C09CA03

Mechanism of action

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, 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 is not known to bind to or

	block other hormone receptors or ion channels known to be important in cardiovascular regulation. Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang 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.
	5.2 Pharmacokinetics Properties: *Absorption* Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours with tablets and 1-2 hours with solution formulation. Mean absolute bioavailability is 23% and 39% with tablets and solution formulation, respectively. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) 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 biotransformed 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. *Excretion* Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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: Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. 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. 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 plasma

	urea, 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 similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea 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. *Paediatric population* Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Microcrystalline Cellulose, Croscarmellose Sodium, Colloidal Anhydrous Silica, Povidone, Magnesium Stearate, Instacoat EHP 250 A10R00391 Pink (Titanium Dioxide, Yellow Iron Oxide, Red Iron Oxide), 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:** Aug 10, 2021