

*[Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]*

[Additional instructions and examples]

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### 1. NAME OF THE MEDICINAL PRODUCT

Amlosartan 5/160 Tablet

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Amlodipine Besilate BP 6.9400 mg equivalent to Amlodipine 5 mg and Valsartan USP 160.0000 mg.

Excipients with known effect:

Ingredient	Reference Standards	to	mg/ Tablet	Function
Microcrystalline Cellulose (102)	BP		107.9600	Diluent
Crospovidone (Type B)	USP-NF		40.0000	Disintegrating Agent
Colloidal Silicon Dioxide (200)	USP-NF		4.1000	Glidant
Magnesium Stearate	BP		9.0000	Lubricant

Coating Materials			
Ingredient	Reference to Standards	mg/ Tablet	Function
Opadry II 85G82999Yellow	In-house	13.1200	Film forming ready-mix polymer
Purified Water**	BP	74.3500	Solvent

### 3. PHARMACEUTICAL FORM

Caplet shaped, yellow colored film coated tablet having a bisect line on one side and 'INCEPTA' engraved on other.

## **4. Clinical particulars**

### **4.1 Therapeutic indications**

Amlosartan is indicated for the treatment of hypertension. This combination drug is not indicated for the initial therapy of hypertension.

### **4.2 Posology and method of administration**

Amlodipine is an effective treatment of hypertension in once daily doses of 2.5 mg to 10 mg while Valsartan is effective in doses of 80 mg to 320 mg. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320 mg tablet once daily as needed to control blood pressure. Amlosartan may be administered with or without food. Amlosartan may be administered with other antihypertensive agents. A patient whose blood pressure is not adequately controlled with Amlodipine alone or with Valsartan alone may be switched to their combination therapy.

Elderly patients: Because of decreased clearance of Amlodipine, therapy should usually be initiated at 2.5 mg.

Renal impairment: No initial dosage adjustment is required for patients with mild or moderate renal impairment. Titrate slowly in patients with severe renal impairment.

Hepatic impairment: No initial dosage adjustment is required for patients with mild or moderate liver insufficiency. Titrate slowly in patients with hepatic impairment.

### **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 Amlosartan 5/160 Tablet with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m<sup>2</sup>).
- 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 warnings 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.

##### *Sodium- and/or volume-depleted patients*

Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Amlosartan 5/160 Tablet 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 Amlosartan 5/160 Tablet or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Amlosartan 5/160 Tablet, 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*

Amlosartan 5/160 Tablet 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 Amlosartan 5/160 Tablet in patients who have had 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 Amlosartan 5/160 Tablet 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 Amlosartan 5/160 Tablet is required for patients with mild to moderate renal impairment (GFR >30 ml/min/1.73 m<sup>2</sup>). 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. Amlosartan 5/160 Tablet 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.

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. Amlosartan 5/160 Tablet has not been studied in any patient population other than hypertension.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### ***Interactions common to the combination***

No drug-drug interaction studies have been performed with Amlosartan 5/160 Tablet 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 diuretic is also used, the risk of lithium toxicity may presumably be increased further with Amlosartan 5/160 Tablet.

*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, ciclosporin) or efflux transporter (ritonavir)*

The results of an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

*Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren*

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting.

*Others*

In monotherapy with valsartan, no interactions of clinical significance have been found with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

## **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 Amlosartan 5/160 Tablet during breast-feeding, therefore Amlosartan 5/160 Tablet 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***

There are no clinical studies on fertility with Amlosartan 5/160 Tablet.

### ***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<sup>2</sup> 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 machines**

No studies on the effects on the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

### Summary of the safety profile

The safety of Amlosartan 5/160 Tablet 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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 Amlosartan 5/160 Tablet	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	--
Nervous system disorders	Confusion	--	Rare	--
	Coordination abnormal	Uncommon	--	--
	Dizziness	Uncommon	Common	--

<b>MedDRA System organ class</b>	<b>Adverse reactions</b>	<b>Frequency Amlosartan 5/160 Tablet</b>	<b>Amlodipine</b>	<b>Valsartan</b>
	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,	--	Very rare	--

<b>MedDRA System organ class</b>	<b>Adverse reactions</b>	<b>Frequency Amlosartan 5/160 Tablet</b>	<b>Amlodipine</b>	<b>Valsartan</b>
Skin and subcutaneous tissue disorders	jaundice			
	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	--	--
Reproductive system and breast disorders General disorders and administration site conditions	Renal failure and impairment	--	--	Not known
	Impotence	--	Uncommon	--
	Erectile dysfunction	Rare	--	--
	Gynaecomastia	--	Uncommon	--
	Asthenia	Common	Uncommon	--
	Discomfort, malaise	--	Uncommon	--
	Fatigue	Common	Common	Uncommon
	Facial oedema	Common	--	--
	Flushing, hot flush	Common	--	--
	Non cardiac chest pain	--	Uncommon	--
Investigations	Oedema	Common	Common	--
	Oedema peripheral	Common	--	--
	Pain	--	Uncommon	--
	Pitting oedema	Common	--	--
	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	<b>Valsartan (mg)</b>					
peripheral oedema	0	40	80	160	320	
<b>Amlodipine</b>	0	3.0	5.5	2.4	1.6	0.9
<b>(mg)</b>	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 Amlosartan 5/160 Tablet 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.

#### Valsartan

Not known      Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

### **4.9 Overdose**

#### *Symptoms*

There is no experience of overdose with Amlosartan 5/160 Tablet. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

#### *Treatment*

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption. Clinically significant hypotension due to Amlosartan 5/160 Tablet 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 Pharmacodynamics properties**

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, combinations; angiotensin II antagonists and calcium channel blockers.

ATC code: C09DB01

## **Mechanism of action**

Amlosartan 5/160 Tablet 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.

### *Placebo-controlled trials*

Over 1,400 hypertensive patients received the product once daily in two placebo-controlled trials. Adults with mild to moderate uncomplicated essential hypertension (mean sitting diastolic blood pressure  $\geq 95$  and  $< 110$  mmHg) were enrolled. Patients with high cardiovascular risks – heart failure, type I and poorly controlled type II diabetes and history of myocardial infarction or stroke within one year – were excluded.

### *Active-controlled trials in patients who were non-responders to monotherapy*

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure  $< 90$  mmHg at the end of the trial) in patients not adequately controlled on valsartan 160 mg in 75% of patients treated with amlodipine/valsartan 10 mg/160 mg and 62% of patients treated with amlodipine/valsartan 5 mg/160 mg, compared to 53% of patients remaining on valsartan 160 mg. The addition of amlodipine 10 mg and 5 mg produced an additional reduction in systolic/diastolic blood pressure of 6.0/4.8 mmHg and 3.9/2.9 mmHg, respectively, compared to patients who remained on valsartan 160 mg only.

A multicentre, randomised, double-blind, active-controlled, parallel-group trial showed normalisation of blood pressure (trough sitting diastolic blood pressure  $< 90$  mmHg at the end of the trial) in patients not adequately controlled on amlodipine 10 mg in 78% of patients treated with amlodipine/valsartan 10 mg/160 mg, compared to 67% of patients remaining on amlodipine 10 mg. The addition of valsartan 160 mg produced an additional reduction in systolic/diastolic blood pressure of 2.9/2.1 mmHg compared to patients who remained on amlodipine 10 mg only.

Amlosartan 10/160 Tablet was also studied in an active-controlled study of 130 hypertensive patients with

mean sitting diastolic blood pressure  $\geq 110$  mmHg and  $< 120$  mmHg. In this study (baseline blood pressure 171/113 mmHg), an Amlsartan 10/160 Tablet regimen of 5 mg/160 mg titrated to 10 mg/160 mg reduced sitting blood pressure by 36/29 mmHg as compared to 32/28 mmHg with a regimen of lisinopril/hydrochlorothiazide 10 mg/12.5 mg titrated to 20 mg/12.5 mg.

In two long-term follow-up studies the effect of Amlsartan 10/160 Tablet was maintained for over one year. Abrupt withdrawal of Amlsartan 10/160 Tablet has not been associated with a rapid increase in blood pressure. Age, gender, race or body mass index ( $\geq 30$  kg/m<sup>2</sup>,  $< 30$  kg/m<sup>2</sup>) did not influence the response to Amlsartan 10/160 Tablet.

Amlsartan 10/160 Tablet has not been studied in any patient population other than hypertension. Valsartan has been studied in patients with post myocardial infarction and heart failure. Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

### ***Amlodipine***

The amlodipine component of Amlsartan 10/160 Tablet 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.

#### *Use in patients with hypertension*

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

#### ***Valsartan***

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT<sub>1</sub>, which is responsible for the known actions of angiotensin II. The increased

plasma levels of angiotensin II following AT<sub>1</sub> receptor blockade with valsartan may stimulate the unblocked receptor subtype AT<sub>2</sub>, which appears to counterbalance the effect of the AT<sub>1</sub> receptor. Valsartan does not exhibit any partial agonist activity at the AT<sub>1</sub> receptor and has much (about 20,000-fold) greater affinity for the AT<sub>1</sub> receptor than for the AT<sub>2</sub> 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.

*Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)*

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an ARB.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and

mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an ARB in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

## **5.2 Pharmacokinetic properties**

### *Linearity*

Amlodipine and valsartan exhibit linear pharmacokinetics.

### *Amlodipine/Valsartan*

Following oral administration of Amlosartan 10/160 Tablet, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Amlosartan 5/160 Tablet are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

### ***Amlodipine***

*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.

### ***Valsartan***

*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 ( $t_{1/2\alpha}$  <1 h and  $t_{1/2\beta}$  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.

### *Special populations*

#### *Paediatric population (age below 18 years)*

No pharmacokinetic data are available in the paediatric population.

#### *Elderly (age 65 years or over)*

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly

patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

#### *Renal impairment*

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan.

#### *Hepatic impairment*

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease exposure (measured by AUC values) to valsartan is twice that found in healthy volunteers (matched by age, sex and weight). Caution should be exercised in patients with liver disease.

### **5.3 Preclinical safety data**

#### **Amlodipine/Valsartan**

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 160mg 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 10mg 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 therat, 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 10mg 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.

## **Amlodipine**

### *Reproductive toxicology*

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<sup>2</sup> 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<sup>2</sup> 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. These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m<sup>2</sup> basis (calculations assume an oral dose of 320 mg/day and a 60kg 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<sup>2</sup> basis (calculations assume an oral dose of 320 mg/day and a 60kg 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 (102)
- Crospovidone (Type B)
- Colloidal Silicon Dioxide (200)
- Magnesium Stearate
- Opadry II 85G82999Yellow
- Purified Water

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

24 months from the date of manufacturing

## **6.4 Special precautions for storage**

Do not store at a temperature above 30°C.

## **6.5 Nature and contents of container <and special equipment for use, administration or implantation>**

Alu/Alu blisters placed in a printed carton. Each pack contains 3 blister strips of 10 Tablets

## **6.6 Special precautions for disposal <and other handling>**

No special requirements.

## **7. <APPLICANT/MANUFACTURER>**

### **Incepta Pharmaceuticals Ltd**

Factory Address: Dewan Idris Road, Bara Rangamatia, Zirabo, Ashulia, Savar, Dhaka, Bangladesh.

Head Office Address: 40, Shahid Tajuddin Ahmed Sarani; Tejgaon I/A, Dhaka-1208; Bangladesh.