**Amval 5mg/80mg**
**Amval 5mg/160mg**
**Amval 10mg/160mg**

**Film Coated Tablets**

## 1. NAME OF THE MEDICINAL PRODUCT

Amval 5mg/80mg Film Coated Tablets
Amval 5mg/160mg Film Coated Tablets
Amval 10mg/160mg Film Coated Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Amval 5mg/80mg Film Coated Tablets:** Each tablet contains 6.934mg of Amlodipine besylate equivalent to Amlodipine 5mg and Valsartan 80mg.

**Amval 5mg/160mg Film Coated Tablets:** Each tablet contains 6.934mg of Amlodipine besylate equivalent to Amlodipine 5mg and Valsartan 160mg.

**Amval 10mg/160mg Film Coated Tablets:** Each tablet contains 13.868mg of Amlodipine besylate equivalent to Amlodipine 10mg and Valsartan 160mg.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablet.

**Amval 5mg/80mg Film Coated Tablets:** Light yellow, round shaped film-coated tablets, debossed with "N" on one side and "7" on the other side.

**Amval 5mg/160mg Film Coated Tablets:** Light yellow, capsule shaped film-coated tablets, debossed with "N 5" on one side and plain on the other side.

**Amval 10mg/160mg Film Coated Tablets:** Light yellow, capsule shaped film-coated tablets, debossed with "N 4" on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of essential hypertension.
Amval is indicated in patients whose blood pressure is not adequately controlled by monotherapy.
Amval is indicated for the initial treatment of hypertension. The choice of Amval for initial treatment should be based on an assessment of the potential benefits and risks.

### 4.2 Posology and method of administration

**General target population**

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to combination therapy with Amval. The recommended dose is one tablet per day. 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 may be switched to Amval containing the same component doses.

For initial therapy the usual starting dose is Amval 5mg/80 mg once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of 10 mg/320 mg per day as needed to control blood pressure. Amval is not recommended as initial therapy in patients with intravascular volume depletion.

The maximum dose is 10mg/320 mg per day.

Both amlodipine and valsartan monotherapy can be taken with or without food. It is recommended to take Amval with some water.

**Special populations**

*Geriatric patients (aged 65 years or above)*
Since both components of the combination are equally well tolerated when used at similar doses in elderly (aged 65 years or above) or younger patients, no dose adjustment of the starting dose is required. Starting with the lowest available dose of amlodipine should be considered. The lowest strength of Amval contains 5 mg of amlodipine.

*Pediatric patients (below 18 years)*
Amval is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

*Renal impairment*
No dosage adjustment is required for patients with mild to moderate renal impairment. Caution is required if severe renal impairment occur.

*Hepatic impairment*
Liver function should be monitored in patients with mild to moderate hepatic impairment. The daily dose of Amval should not exceed 5/80mg in patients with mild to moderate hepatic impairment without cholestasis. Amval is contraindicated in severe hepatic impairment. Starting with the lowest available dose of amlodipine should be considered. The lowest strength of Amval contains 5 mg of amlodipine.

**4.3 Contraindications**

- Known hypersensitivity to the amlodipine, valsartan or to any of the excipients.
- Pregnancy.
- Severe hepatic impairment; biliary cirrhosis and cholestasis.
- Concomitant use of angiotensin receptor antagonists (ARBs) - including valsartan - or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren in patients with

Type 2 diabetes.

**4.4 Special warnings and precautions for use**

**Patients with sodium- and/or volume depletion**
Excessive hypotension was seen in 0.4% of patients with uncomplicated hypertension treated with Amval 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 Amval or close medical supervision at the start of treatment is recommended.

If hypotension occurs with Amval, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once blood pressure has been stabilized.

**Hyperkalemia**
Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

**Patients with renal artery stenosis**
Amval should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

**Patients with renal impairment**
No data is available for severe cases (creatinine clearance < 10 mL/min.) and caution is therefore advised. No dosage adjustment of Amval is required for patients with mild to moderate renal impairment.
The use of ARBs - including valsartan - or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min).

**Patients with kidney transplantation**
To date there is no experience of the safe use of Amval in patients who have had a recent kidney transplantation.

**Patients with hepatic impairment**
Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. In patient with mild to moderate hepatic impairment without cholestasis, Amval should be used with caution and careful monitoring of liver function tests should be performed. The daily dose of Amval should not exceed 5/80mg. Patients with severe hepatic impairment, biliary cirrhosis or cholestasis should not take Amval.

**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. Amval should be immediately discontinued in patients who

develop angioedema, and Amval should not be re-administered.

**Patients with heart failure/post-myocardial infarction**
In general, calcium channel blockers including amlodipine should be used with caution in patients with serious congestive heart failure (New York Heart Association (NYHA) functional class III-IV).

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 angiotensin converting enzyme inhibitors or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

**Patients with acute myocardial infarction**
Worsening angina pectoris and acute myocardial infarction can develop after starting or increasing the dose of amlodipine, particularly in patients with severe obstructive coronary artery disease.

**Patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy**
As with all other vasodilators, special caution is required when using amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

**Dual Blockade of the Renin-Angiotensin System (RAS)**
Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren (see section INTERACTIONS, subsection dual blockade of the RAS).

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

**Amlodipine**
*Simvastatin:* Co-administration of multiple doses of 10 mg of 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.

*CYP3A4 Inhibitors:* Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 1.6-fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

*Grapefruit Juice:* The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition. However, co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

*CYP3A4 Inducers:* No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when

amlodipine is co-administered with CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, maalox (Aluminium hydroxide gel, Magnesium hydroxide and Simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

**Valsartan**

*Dual blockade of the renin-angiotensin system (RAS) with ARBs, ACEIs or aliskiren:* The concomitant use of ARBs, including valsartan, with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalaemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Amval and other agents that affect the RAS.

The concomitant use of ARBs - including valsartan - or of ACEIs with aliskiren, should be avoided in patients with severe renal impairment (GFR < 30 mL/min).

The concomitant use of ARBs including valsartan, or ACEIs, with aliskiren is contraindicated in patients with Type 2 diabetes mellitus.

*Potassium:* Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

*Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors):* When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

*Lithium:* Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or angiotensin II receptor antagonists including Amval. 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 Amval.

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

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

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*
As for any drug that acts directly on the RAAS, Amval must not be used during pregnancy. Due to the mechanism of action of angiotensin II antagonists, a risk to the foetus cannot be excluded. Administration of angiotensin converting enzyme (ACE) inhibitors (a specific class of drugs acting on the renin- angiotensin- aldosterone system, RAAS) to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have inadvertently taken valsartan.

There are no adequate clinical data with amlodipine in pregnant women. The potential risk to humans is unknown.

If pregnancy is detected during therapy, Amval must be discontinued as soon as possible.

*Clinical considerations*
*Disease-associated maternal and/or embryo/fetal risk*
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death.

*Fetal/Neonatal Risk*
Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension and death.

In case of accidental exposure to ARB therapy, appropriate fetal monitoring should be considered.
Infants whose mothers have taken ARB therapy in the first trimester, should be closely observed for hypotension.

*Breastfeeding*
It is not known whether valsartan is excreted in human milk. It is reported that 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. Valsartan was excreted in the milk of lactating rats. It is therefore not advisable for women who are breast-feeding to use Amval.

*Fertility*
There is no information on the effects of amlodipine or valsartan on human fertility

## 4.7 Effects on ability to drive and use machines

Patients taking Amval 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

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; common; uncommon; rare; very rare; not known.

| **MedDRA System organ class** | **Adverse reactions** | **Frequency** | | |
|---|---|---|---|---|
| | | **Amval** | **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 | - |

| MedDRA System organ class | Adverse reactions | Frequency | | |
|---|---|---|---|---|
| | | **Amval** | **Amlodipine** | **Valsartan** |
| | 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, upper abdominal pain | 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 |

| MedDRA System organ class | Adverse reactions | Frequency | | |
|---|---|---|---|---|
| | | **Amval** | **Amlodipine** | **Valsartan** |
| | 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 | 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 Amval combination than in those who received amlodipine alone. 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 Amval 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 Amval as well.

*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 liverfunction 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 overdosage with Amval yet. The major symptom of overdosage with valsartan is possibly pronounced hypotension with dizziness. Overdosage with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia.

Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

**Treatment**
Clinically significant hypotension due to amlodipine overdosage 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.
If the 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. 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: Angiotensin II antagonists, plain (valsartan) combinations with dihydropyridine derivatives (amlodipine), ATC code: C09DB01.

*Mechanism of action*
Amval 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 (Ang II) antagonist class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

*Amlodipine*
The amlodipine component of Amval 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 blood pressure. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine 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 vasodilatation 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 experiences on electrocardiographic parameters were observed.

Amlodipine has demonstrated beneficial clinical effects in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

*Valsartan*
Valsartan is an orally active, potent, and specific angiotensin II receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 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 cough. 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 cough 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 reduction of 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 reduction of 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.

In patients with chronic heart failure (NYHA class II-IV), valsartan has been demonstrated to significantly reduce hospitalizations in patients with chronic heart failure (NYHA class II-IV). The benefits were greatest in patients not receiving either an ACE inhibitor or a beta blocker. In post-MI patients, valsartan has also been shown to reduce cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction

following myocardial infarction.

**5.2 Pharmacokinetic properties**

**Linearity**
Valsartan and amlodipine exhibit linear pharmacokinetics.

**Amlodipine**
*Absorption*
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 to 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.

Amlodipine crosses the placenta and is excreted into breast milk.

*Biotransformation*
Amlodipine is extensively (approximately 90%) metabolized 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 the 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 group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in 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 liters indicating that valsartan is not distributed 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 (1/2α <1h and t 1/2 ß about 9 h). Valsartan is primarily eliminated unchanged 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.

**Valsartan/Amlodipine**
Following oral administration of Amval peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of Amval are equivalent to the bioavailability of valsartan and amlodipine when administered as individual tablets.

**Special populations**

*Geriatric patients*
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly patients.

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance.

*Renal impairment*
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Patients with mild to moderate renal impairment may therefore receive the usual initial dose.

*Hepatic impairment*
Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC of approximately 40-60%. In a small number of patients with mild to moderate hepatic impairment given single doses of 5 mg, amlodipine half-life has been prolonged. Worsening of liver function test values may occur.

About 70% of the absorbed valsartan dose is excreted in the bile, mainly as unchanged compound. The AUC with valsartan has been observed to approximately double in patients with mild or moderate hepatic impairment including patients with biliary obstructive disorders. There are no data available on the use of valsartan in patients with severe hepatic dysfunction.

Care should be exercised in patients with liver disease.

## 6. PHARMACOLOGICAL PROPERTIES
### 6.1 List of excipients

Tablet core:
Microcrystalline Cellulose, Crospovidone, Povidone, Colloidal Silicon Dioxide, Magnesium Stearate

Film-coat:
Opadry II Complete Film Coating System 85F12273 Yellow (5mg/80mg & 5mg/160mg), Opadry II Complete Film Coating System 85F62534 Yellow (10mg/160mg)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

Please refer to the expiry date on the product labels.

### 6.4 Special precautions for storage

Store below 30°C. Protect from moisture. Store in the original package.

### 6.5 Nature and contents of container

Alu/ Alu blisters of 1 x 10's, 3 x 10's, 10 x 10's, 50 x 10's, 100 x 10's, 1 x 14's, 2 x 14's, 4 x 14's, 6 x 14's, 8 x 14's, 12 x 14's in blister form packed in the outer carton. Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MANUFACTURER

**Manufactured by:**
Novugen Pharma Sdn. Bhd.
No. 27, Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1,
71760 Bandar Baru Enstek,
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**Product Registration Holder:**
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## 8 DATE OF REVISION

03/06/2022

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