# Onato®-V

(Amlodipine Besylate + 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.

## 1. NAME OF THE PRODUCT

**Onato®-V** (Amlodipine Besylate + Valsartan) 5/80mg Tablets
**Onato®-V** (Amlodipine Besylate + Valsartan) 5/160mg Tablets
**Onato®-V** (Amlodipine Besylate + Valsartan) 10/160mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Onato®-V 5/80mg Tablets**
Each film coated tablet contains:
Amlodipine Besylate Ph. Eur. equivalent to Amlodipine.....5mg
Valsartan USP.....80mg

**Onato®-V 5/160mg Tablets**
Each film coated tablet contains:
Amlodipine Besylate Ph. Eur. equivalent to Amlodipine…....5mg
Valsartan USP.....160mg

**Onato®-V 10/160mg Tablets**
Each film coated tablet contains:
Amlodipine Besylate Ph. Eur. equivalent to Amlodipine…..10mg
Valsartan USP.....160mg

## 3. PHARMACEUTICAL FORM

Film-coated tablet

**Appearance:**
**Onato®-V 5/80mg Tablets:** Yellow color oblong shaped film coated tablet, plain on both sides.
**Onato®-V 5/160mg Tablets:** Pink color oval shaped film coated tablet, plain on both sides.
**Onato®-V 10/160mg Tablets:** Green color oval shaped film coated tablet, plain on both sides.

# 4. CLINICAL PARTICULARS

## 4.1. THERAPEUTIC INDICATIONS:

Treatment of essential hypertension.

**Onato®-V** is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

## 4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

**Posology:**

The recommended dose of **Onato®-V** is one tablet per day.

**Onato®-V** 5mg/80mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone.

**Onato®-V** 5mg/160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone.

**Onato®-V** 10mg/160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10mg or valsartan 160mg alone or with **Onato®-V** 5mg/160mg.

**Onato®-V** can be used with or without food.

Individual dose titration with the components (i.e. amlodipine and valsartan) is recommended before changing to the fixed dose combination. When clinically appropriate, direct change from monotherapy to the fixed-dose combination may be considered.

For convenience, patients receiving valsartan and amlodipine from separate tablets/capsules may be switched to **Onato®-V** containing the same component doses.

**Special Population:**

**Renal impairment:** No dosage adjustment is required for patients with mild to moderate renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

**Hepatic impairment: Onato®-V** is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering **Onato®-V** to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients with hepatic impairment to amlodipine or **Onato®-V**, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

**Elderly (age 65 years or over):** In elderly patients, caution is required when increasing the dosage. When switching eligible elderly hypertensive patients to amlodipine or **Onato®-V**, the lowest available dose of amlodipine monotherapy or of the amlodipine component, respectively, should be used.

**Paediatric population:** The safety and efficacy of **Onato®-V** in children aged below 18 years have not been established. No data are available.

**Method of administration:**
For oral use only.
It is recommended to take **Onato®-V** with some water.

## 4.3. CONTRAINDICATIONS:

- Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis or cholestasis.
- Concomitant use of Amlodipine Besylate/ Valsartan with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60ml/min/1.73m$^2$)
- Second and third trimesters of pregnancy.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high-grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

## 4.4. SPECIAL 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:** 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 Amlodipine Besylate/ Valsartan or close medical supervision at the start of treatment is recommended. If hypotension occurs with Amlodipine Besylate/ Valsartan, 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 stabilized.

**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:** Amlodipine Besylate/ Valsartan 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 Amlodipine Besylate/ Valsartan in patients who have had a recent kidney transplantation.

**Hepatic impairment:** Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function, dosage recommendations have not been established. Particular caution should be exercised when administering Amlodipine Besylate/ Valsartan 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 Amlodipine Besylate/ Valsartan is required for patients with mild to moderate renal impairment (GFR >30ml/min/1.73m$^2$). Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

**Primary hyperaldosteronism:** Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin angiotensin system is affected by the primary disease.

**Angioedema:** Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced angioedema with other medicinal products, including ACE inhibitors. Amlodipine Besylate/ Valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.

**Intestinal angioedema:** Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including valsartan. These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

**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. 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):** 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 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.

## 4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

**Interactions common to the combination:**

No drug-drug interaction studies have been performed with Amlodipine Besylate/ Valsartan 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:*** It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

***Dantrolene (infusion):*** 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.

***Tacrolimus:*** There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

**To be taken into account with concomitant use:**

***Others:*** Amlodipine has no effect on the pharmacokinetics of atorvastatin, digoxin, warfarin or ciclosporin.

**Interactions linked to valsartan:**

**Concomitant use not recommended:**

***Lithium:*** 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 Amlodipine Besylate/ Valsartan.

***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 (>3g/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):*** 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:*** Dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

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

## 4.6. FERTILITY, PREGNANCY AND LACTATION:

**Fertility:** There are no clinical studies on fertility with Amlodipine Besylate/ Valsartan.

**Pregnancy:**

***Amlodipine:*** The safety of amlodipine in human pregnancy has not been established. 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:***

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|---|
| 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. |

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 Amlodipine Besylate/

Valsartan during breast-feeding, therefore Amlodipine Besylate/ 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.

## 4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients taking Amlodipine Besylate/ Valsartan 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:

**Tabulated list of adverse reactions:**

The adverse reactions ranked under headings of system organ class and frequency using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data) for VTEp, NVAF, and VTEt respectively. Rare (< 1/10,000); not known (cannot be estimated from the available data).

| System Organ Class | Adverse reactions | Frequency | | |
|---|---|---|---|---|
| | | Onato®-V | 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 | Hyperglycaemia | – | Very rare | – |
| | Hyponatraemia | Uncommon | – | – |
| Psychiatric disorders | Depression | – | Uncommon | – |
| | Anxiety | Rare | – | – |

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|---|---|---|---|---|
| | Insomnia / sleep disorders | – | Uncommon | – |
| | Mood swings | – | Uncommon | – |
| | Confusion | – | Rare | – |
| Nervous system disorders | Coordination abnormal | Uncommon | – | – |
| | Dizziness | Uncommon | Common | – |
| | Dizziness postural | Uncommon | – | – |
| | Dysgeusia | – | Uncommon | – |
| | Extrapyramidal disorder | – | 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 | – |
| | Abdominal discomfort, | Uncommon | Common | Uncommon |

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|---|---|---|---|---|
| Gastro-intestinal disorders | abdominal pain upper | | | |
| | Change of bowel habit | – | Uncommon | – |
| | Constipation | Uncommon | – | – |
| | Diarrhoea | Uncommon | Uncommon | – |
| | Dry mouth | Uncommon | Uncommon | – |
| | Dyspepsia | – | Uncommon | – |
| | Gastritis | – | Very rare | – |
| | Gingival hyperplasia | – | Very rare | – |
| | Intestinal angioedema | – | – | Very rare |
| | Nausea | Uncommon | Common | – |
| | Pancreatitis | – | Very rare | – |
| | Vomiting | – | Uncommon | – |
| Hepatobiliary disorders | Liver function test abnormal, including blood bilirubin increase | – | Very rare | Not known |
| | Hepatitis | – | Very rare | – |
| | Intrahepatic cholestasis, jaundice | – | Very rare | – |
| Skin and subcutaneous tissue disorders | Alopecia | – | Uncommon | – |
| | Angioedema | – | Very rare | Not known |
| | Dermatitis bullous | – | – | Not known |
| | Erythema | Uncommon | – | – |
| | Erythema multiforme | – | Very rare | – |
| | Exanthema | Rare | Uncommon | – |
| | Hyperhidrosis | Rare | Uncommon | – |
| | Photosensitivity reaction | – | Uncommon | – |
| | Pruritus | Rare | Uncommon | Not known |
| | Purpura | – | Uncommon | – |
| | Rash | Uncommon | Uncommon | Not known |
| | Skin discolouration | – | Uncommon | – |
| | Urticaria and other forms of rash | – | Very rare | – |
| | Exfoliative dermatitis | – | Very rare | – |
| | Stevens-Johnson syndrome | – | Very rare | – |
| | Quincke oedema | – | Very rare | – |
| | Toxic epidermal necrolysis | – | Not known | – |
| Musculo-skeletal and connective | Arthralgia | Uncommon | Uncommon | – |
| | Back pain | Uncommon | Uncommon | – |
| | Joint swelling | Uncommon | – | – |
| | Muscle spasm | Rare | Uncommon | – |

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|---|---|---|---|---|
| tissue disorders | Myalgia | – | Uncommon | Not known |
| | Ankle swelling | – | Common | – |
| | Sensation of heaviness | Rare | – | – |
| Renal and urinary disorders | Blood creatinine increased | – | – | Not known |
| | Micturition disorder | – | Uncommon | – |
| | Nocturia | – | Uncommon | – |
| | Pollakiuria | Rare | Uncommon | – |
| | Polyuria | Rare | – | – |
| | Renal failure and impairment | – | – | Not known |
| Reproductive system and breast disorders | Impotence | – | Uncommon | – |
| | Erectile dysfunction | Rare | – | – |
| | Gynaecomastia | – | Uncommon | – |
| General disorders and administration site conditions | Asthenia | Common | Uncommon | – |
| | Discomfort, malaise | – | Uncommon | – |
| | Fatigue | Common | Common | Uncommon |
| | Facial oedema | Common | – | – |
| | Flushing, hot flush | Common | – | – |
| | Non cardiac chest pain | – | Uncommon | – |
| | Oedema | Common | Common | – |
| | Oedema peripheral | Common | – | – |
| | Pain | – | Uncommon | – |
| | Pitting oedema | Common | – | – |
| Investigations | Blood potassium increased | – | – | Not known |
| | Weight increase | – | Uncommon | – |
| | Weight decrease | – | Uncommon | – |

## 4.9. OVERDOSE:

**Symptoms:** There is no experience of overdose with Amlodipine Besylate/ Valsartan. 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, including shock with fatal outcome, have been reported with amlodipine. Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

**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 Amlodipine Besylate/ Valsartan overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. PHARMACODYNAMIC PROPERTIES:

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

**ATC code:** C09DB01

**Onato®-V** 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.

**Mechanism of action:**

***Amlodipine:*** The amlodipine component of **Onato®-V** 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.

***Valsartan:*** Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype $AT_1$, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following $AT_1$ receptor blockade with valsartan may stimulate the unblocked receptor subtype $AT_2$, which appears to counterbalance the effect of the $AT_1$ receptor. Valsartan does not exhibit any partial agonist activity at the $AT_1$ receptor and has much (about 20,000-fold) greater affinity for the $AT_1$ receptor than for the $AT_2$ receptor. Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.

***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.

## 5.2. PHARMACOKINETICS PROPERTIES:

***Linearity:*** Amlodipine and valsartan exhibit linear pharmacokinetics.

**Amlodipine/Valsartan:**

Following oral administration of Amlodipine Besylate/ Valsartan, peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively. The rate and extent of absorption of Amlodipine Besylate/ Valsartan 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.

***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 exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration ($C_{max}$) by about 50%. Valsartan can 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 d $t_{1/2ß}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

## 5.3. PRECLINICAL SAFETY DATA:

**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 10mg 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 160mg valsartan).

An increased incidence and severity of renal tubular basophilia/hyalinization, 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 160mg valsartan and 10mg amlodipine. Similar changes were found in the valsartan alone group (exposure 8.5–11.0 times the clinical dose of 160mg valsartan).

In an embryo-foetal development study in the rat, increased incidences of dilated ureters, malformed sternebrae, and unossified forepaw phalanges were noticed at exposures of about 12 (valsartan) and 10 (amlodipine) times the clinical doses of 160mg valsartan and 10mg amlodipine. Dilated ureters were also found in the valsartan alone group (exposure 12 times the clinical dose of 160mg 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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1. LIST OF EXCIPIENTS:

**Onato®-V 5/80mg Tablets:**

***Tablet Core:***

- Microcrystalline Cellulose
- Lactose Monohydrate
- Maize Starch
- Sodium Starch Glycolate
- Magnesium Stearate
- Croscarmellose Sodium
- Copovidone
- Silicon Dioxide Fumed

***Film Coating:***

- Hydroxypropyl Methyl Cellulose
- Poly Ethylene Glycol
- Poly Vinyl Pyrrolidone

- Talcum Powder
- Titanium Dioxide
- Simethicone LVA
- Tartrazine Yellow Lake Color
- Isopropyl Alcohol
- Purified Water

**Onato®-V 5/160mg Tablets:**

***Tablet Core:***

- Microcrystalline Cellulose
- Lactose Monohydrate
- Maize Starch
- Sodium Starch Glycolate
- Magnesium Stearate
- Croscarmellose Sodium
- Copovidone
- Silicon Dioxide Fumed

***Film Coating:***

- Hydroxypropyl Methyl Cellulose
- Poly Ethylene Glycol
- Poly Vinyl Pyrrolidone
- Talcum Powder
- Titanium Dioxide
- Simethicone LVA
- Allura Red Lake Color
- Isopropyl Alcohol
- Purified Water

**Onato®-V 10/160mg Tablets:**

***Tablet Core:***

- Microcrystalline Cellulose
- Lactose Monohydrate
- Maize Starch
- Sodium Starch Glycolate
- Magnesium Stearate
- Croscarmellose Sodium
- Copovidone
- Silicon Dioxide Fumed

***Film Coating:***

- Hydroxypropyl Methyl Cellulose

- Poly Ethylene Glycol
- Poly Vinyl Pyrrolidone
- Talcum Powder
- Titanium Dioxide
- Simethicone LVA
- Apple Green Lake Color
- Isopropyl Alcohol
- Purified Water

**6.2. INCOMPATIBILITIES:**
Not applicable

**6.3. SHELF LIFE:**
See expiry on the pack.

**6.4. SPECIAL PRECAUTIONS FOR STORAGE:**
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

**6.5. NATURE AND CONTENTS OF CONTAINER:**
**Onato®-V 5/80mg Tablets:** Alu/Alu blister packing, pack size is 14's.
**Onato®-V 5/160mg Tablets:** Alu/Alu blister packing, pack size is 14's.
**Onato®-V 10/160mg Tablets:** Alu/Alu blister packing, pack size is 14's.

**6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:**
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**6.7. DRUG PRODUCT SPECIFICATIONS:**
**Onato®-V 5/80mg Tablets:** USP Specs.
**Onato®-V 5/160mg Tablets:** USP Specs.
**Onato®-V 10/160mg Tablets:** USP Specs.

## 7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
**SAMI Pharmaceuticals (Pvt.) Ltd.**
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

## 8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

**Onato®-V 5/80mg Tablets:** 088212

**Onato®-V 5/160mg Tablets:** 088213
**Onato®-V 10/160mg Tablets:** 088214

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

**Onato®-V 5/80mg Tablets:** 14th March, 2018
**Onato®-V 5/160mg Tablets:** 14th March, 2018
**Onato®-V 10/160mg Tablets:** 14th March, 2018

## 10. DATE OF REVISION OF THE TEXT

# اُناٹو-وی ٹیبلٹ

(ایملوڈیپین بیسیلیٹ + والسارٹن)

## ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔