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Onato®-V Tablets

(Amlodipine Besylate + Valsartan)

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue Onato®-V as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus.

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

PHARMACEUTICAL FORM

Tablet

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS:

Treatment of essential hypertension. Onato®-V tablet is indicated in adults whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.

POSOLOGY AND METHOD OF ADMINISTRATION:

Posology: The recommended dose of Onato®-V tablet is one tablet per day. Onato®-V tablet 5mg/80mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone.
Onato®-V tablet 5mg/160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone.
Onato®-V tablet 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 tablet 5mg/160mg.
Onato®-V tablet 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.
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 tablet is contraindicated in patients with severe hepatic impairment. Caution should be exercised when administering to patients with hepatic impairment or biliary obstructive disorders.
Elderly (age 65 years or over): Caution is required when increasing the dosage.
Paediatric population: The safety and efficacy in children aged below 18 years have not been established.

Method of administration: Oral use: It is recommended to take Onato®-V tablet with some water.

CONTRAINDICATIONS

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

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.
Hyperkalaemia: Caution is advised. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicinal products (heparin, etc.)
Renal artery stenosis and Kidney transplantation: Should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis. No experience of the safe use in patients who have had a recent kidney transplantation.
Hepatic impairment: Particular caution should be exercised when administering 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 80mg valsartan.
Renal impairment: No dosage adjustment is required for patients with mild to moderate renal impairment (GFR >30 ml/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: Onato®-V tablet should be discontinued immediately in patients who develop angioedema and should not be re-administered.
Heart failure/post-myocardial infarction: Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure.
Aortic and mitral valve stenosis: 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): Concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure) therefore not recommended.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Interactions common to the combination.
Other antihypertensive agents: Commonly used antihypertensive agents (e.g. alpha blockers, diuretics) and other medicinal products may increase the antihypertensive effect of the combination. Concomitant use not recommended.
Grapefruit or grapefruit juice: Caution required with concomitant use
CYP3A4 inhibitors: 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. Clinical monitoring and dose adjustment may thus be required.
Simvastatin: It is recommended to limit the dose of simvastatin to 20mg daily in patients on amlodipine.
Dantrolene (infusion): It is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia. Interactions linked to valsartan, Concomitant use not recommended.
Lithium: Careful monitoring of serum lithium levels is recommended during concomitant use.
Caution required with concomitant use: Monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.
Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren: 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.

FERTILITY, PREGNANCY AND LACTATION:

Fertility There are no clinical studies on fertility.
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 fetus.
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.
Lactation: Amlodipine is excreted in human milk. Onato®-V tablet is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a new born or preterm infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients taking Onato®-V tablet and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur. Amlodipine can have

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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

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.

Amlodipine/Valsartan:
Uncommon: Anorexia, hypercalcaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia,
coordination abnormal, dizziness, postural dizziness, paraesthesia, somnolence, visual impairment, vertigo, palpitations, tachycardia, orthostatic hypotension, cough, pharyngolaryngeal pain, abdominal discomfort, abdominal pain upper, constipation, diarrhea, dry mouth, nausea, erythema, rash, arthralgia, joint swelling and back pain.
Rare: Hypersensitivity, anxiety, visual disturbance, tinnitus, syncope, hypotension, exanthema, hyperhidrosis, pruritis, muscle spasm, sensation of heaviness, pollakiuria, polyuria and erectile dysfunction.

Amlodipine:
Common: Dizziness, headache, somnolence, palpitations, flushing, abdominal discomfort, abdominal pain upper, nausea, ankle swelling, fatigue and oedema.
Uncommon: Depression, insomnia/sleep disorders, mood swings, dysgeusia, paraesthesia, syncope, tremor, hypoesthesia, visual disturbance, visual impairment, tinnitus, hypotension, dysponea, rhinitis, change of bowel habit, diarrhoea, dry mouth, dyspepsia, vomiting, alopecia, exanthema, hyperhidrosis, photosensitivity reaction, pruritus, purpura, rash, skin discolouration, arthralgia, back pain, muscle spasm, myalgia, micturition disorder, nocturia, pollakiuria, impotence, gynaecomastia, asthenia, discomfort, malaise, non-cardiac chest pain, pain, weight increase or decrease.
Rare: Confusion.
Very rare: Leukocytopenia, thrombocytopenia, sometimes with purpura, hypersensitivity, hyperglycaemia, hypertonia, peripheral neuropathy, neuropathy, arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation), myocardial infarction, vasculitis, cough, gastritis, gingival hyperplasia, pancreatitis, liver function test abnormal, including blood bilirubin increase, hepatitis, intrahepatic cholestasis, jaundice, angioedema, erythema multiforme, urticaria and other forms of rash, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity.
Valsartan:
Uncommon: Vertigo, cough, abdominal discomfort, abdominal pain upper, fatigue

OVERDOSE:
If ingestion is recent, induction of vomiting or gastric lavage may be considered. 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.

PHARMACOLOGICAL PROPERTIES

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
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.

Mechanism of action:
Amlodipine: 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 AT1, which is responsible for the known actions of angiotensin II. Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.

PHARMACOKINETIC PROPERTIES:
Linearity: Amlodipine and valsartan exhibit linear pharmacokinetics.
Amlodipine/Valsartan: Following oral administration peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6–8 hours, respectively.
Amlodipine:
Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6–12 hours. 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. 10% 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%.
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.
Elimination: Valsartan shows multi exponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½ß}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
Onato®-V 5/80mg tablets in a pack of 14's
Onato®-V 5/160mg tablets in a pack of 14's
Onato®-V 10/160mg tablets in a pack of 14's

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of the reach of children.
Avoid exposure to heat, light and humidity.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Store in the original package in order to protect from moisture.

Full Prescribing Information available on www.samipharmapk.com

اُناٹو-وی ٹیبلٹ

(ایملوڈیپین بیسیلیٹ+والسارٹن)

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 ہوجائیگی۔

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