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Onato®-V HCT Tablets

(Amlodipine Besylate + Valsartan + Hydrochlorothiazide)

WARNING: FETAL TOXICITY
When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing foetus.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Onato®-V HCT Tablet 5mg/160mg/12.5mg
Each film coated tablet contains:
Amlodipine (as Besylate) Ph. Eur.....5mg
Valsartan USP.....160mg
Hydrochlorothiazide BP.....12.5mg

Onato®-V HCT Tablet 5mg/160mg/25mg
Each film coated tablet contains:
Amlodipine (as Besylate) Ph. Eur.....5mg
Valsartan USP.....160mg
Hydrochlorothiazide BP.....25mg

Onato®-V HCT Tablet 10mg/160mg/12.5mg
Each film coated tablet contains:
Amlodipine (as Besylate) Ph. Eur.....10mg
Valsartan USP.....160mg
Hydrochlorothiazide BP.....12.5mg

Onato®-V HCT Tablet 10mg/160mg/25mg
Each film coated tablet contains:
Amlodipine (as Besylate) Ph. Eur.....10mg
Valsartan USP.....160mg
Hydrochlorothiazide BP.....25mg

Onato®-V HCT Tablet 10mg/320mg/25mg
Each film coated tablet contains:
Amlodipine (as Besylate) Ph. Eur.....10mg
Valsartan USP.....320mg
Hydrochlorothiazide BP.....25mg

PHARMACEUTICAL FORM: Tablet

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS: Indicated for treatment of hypertension as substitution therapy in adults whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation. This fixed combination drug is not indicated for the initial therapy of hypertension.

POSOLOGY AND METHOD OF ADMINISTRATION:
Posology: Recommended dose is one tablet per day, preferably in the morning. Before switching to Onato®-V HCT patients should be controlled on stable doses of the monocomponents taken at the same time. The dose should be based on the doses of the individual components of the combination at the time of switching. The maximum recommended dose is 10mg/320mg/25mg.

Special Population:
Renal impairment: No adjustment of the initial dose is required for mild to moderate renal impairment. Contraindicated in anuria and severe renal impairment due to hydrochlorothiazide component.
Hepatic impairment: Contraindicated in severe hepatic impairment. Not suitable in mild to moderate hepatic impairment without cholestasis as the maximum recommended dose is 80mg valsartan. Dose recommendations for amlodipine have not been established in patients with mild to moderate hepatic impairment. Lowest available dose of the amlodipine component should be used.
Elderly (age 65 years or over): Caution, including frequent monitoring of blood pressure, is recommended, particularly at the maximum dose of Onato®-V HCT 10mg/320mg/25mg.
Paediatric population: No relevant use for the indication of essential hypertension.
Heart failure and coronary artery disease: Caution advised particularly at the maximum dose; amlodipine/ valsartan/hydrochlorothiazide 10mg/320mg/25mg.

Method of Administration: Oral use. Can be taken with or without food. Tablets should be swallowed whole with some water.

CONTRAINDICATIONS:
- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients.
- Second and third trimesters of pregnancy.
- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m2), anuria and patients undergoing dialysis.
- Concomitant use with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m2). Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricemia.
- 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.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Safety and efficacy of amlodipine in hypertensive crisis have not been established.
Sodium-and/or volume-depleted patients: Symptomatic hypotension may occur in sodium-depleted and/or volume-depleted patients after initiation of treatment and therefore, should be used only after correction of any pre-existing sodium and/or volume depletion. Treatment can be continued once blood pressure has been stabilised.
Serum electrolyte changes: Periodic determination of serum electrolytes and potassium should be performed at appropriate intervals in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.
Hydrochlorothiazide: Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia; If hypokalaemia/ hyponatraemia develops during hydrochlorothiazide therapy, discontinue this combination.
Renal impairment: Serum electrolytes should be periodically monitored (including potassium), creatinine and uric acid serum levels is recommended.
Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan.
Renal artery stenosis: Should be used with caution in patients with unilateral or bilateral renal artery stenosis.
Angioedema: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue, is known to occur in patients treated with valsartan.
Heart failure and coronary artery disease/post-myocardial infarction: ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. 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: Special caution is indicated in patients.
Primary hyperaldosteronism: Not recommended in this population.
Systemic lupus erythematosus (SLF): Thiazide diuretics, including hydrochlorothiazide, are known to exacerbate or activate systemic lupus erythematosus.
Other metabolic disturbances: Thiazide diuretics, including hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. Contraindicated in symptomatic hyperuricaemia.
Photosensitivity: If photosensitivity reaction occurs during treatment with Onato®-V HCT , it is recommended to stop the treatment.
Choroidal effusion, acute myopia and secondary acute angle-closure glaucoma: Hydrochlorothiazide, has been associated with an idiosyncratic reaction resulting in choroidal effusion with visual field defect, acute transient myopia and acute angle-closure glaucoma. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS): ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.
Non-melanoma skin cancer: Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with increasing cumulative dose of hydrochlorothiazide exposure is known to occur.

INTERACTIONS WITH MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS: Concomitant use not recommended:
- **Valsartan/HCT and Lithium:** Reversible increases in serum lithium concentrations and toxicity is known to occur.
- **Valsartan/HCT and Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels:** Frequent monitoring of potassium plasma levels is advised.
- **Amlodipine and grapefruit juice:** Not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use:
- **Amlodipine and CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir):** May give rise to significant increase in amlodipine exposure. Clinical monitoring and dose adjustment may be required.
- **Amlodipine and CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum [St. John's wort]):** Plasma concentration of amlodipine may vary; 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).
- **Amlodipine and Simvastatin:** If simvastatin is co-administered with amlodipine, do not exceed doses greater than 20mg daily of simvastatin.
- **Amlodipine and Dantrolene:** Risk of hyperkalaemia; co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
- **Valsartan/HCT and NSAIDs:** May attenuate the antihypertensive effect. May lead to worsening of renal function and an increase in serum potassium; Monitoring of renal function at the beginning of the treatment as well as adequate hydration recommended.
- **Valsartan and Inhibitors of the uptake transporter (rifampicin, cyclosporin) or efflux transporter (ritonavir):** Systemic exposure of valsartan maybe increased.
- **HCT and Alcohol, barbiturates or narcotics:** May potentiate orthostatic hypotension.
- **HCT and Amatadine:** May increase the risk of adverse reactions caused by amantadine.
- **HCT and Anticholinergic agents and other medicinal products affecting gastric motility:** Bioavailability of thiazide-type, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.
- **HCT and Antidiabetic agents (e.g. insulin and oral antidiabetic agents):** Thiazides may alter glucose tolerance; dose adjustment of the antidiabetic may be necessary.
- **HCT and Metformin:** Metformin should be used with caution.
- **HCT and Beta blockers and diazoxide:** May increase the risk of hyperglycaemia.
- **HCT and Cyclosporin:** May increase the risk of hyperuricaemia and gout-type complications.
- **HCT and Cytotoxic agents:** May reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
- **HCT and Digitalis glycosides:** Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac

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arrhythmias.
- **HCT and Iodine contrasting agents:** There is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
- **HCT and Ion exchange resins:** Absorption of HCT is decreased by cholestyramine or colestipol; may result in sub-therapeutic effects of thiazide diuretics.
- **HCT and Medicinal products affecting serum potassium level:** Hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives or antiarrhythmics.
- **HCT and Medicinal products affecting serum sodium level:** Hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc.
- **HCT and Medicinal products that could induce torsades de pointes:** Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution in particular. Class Ia and Class III antiarrhythmics and some antipsychotics.
- **HCT and Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol):** Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
- **HCT and Methyldopa:** Haemolytic anaemia is known to occur.
- **HCT and Non-depolarising skeletal muscle relaxants (e.g. tubocurarine):** Thiazides, including HCT, potentiate the action of curare derivatives.
- **HCT and Other anti-hypertensive medicinal products:** Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors [DRIs]).
- **HCT and Pressor amines (e.g. noradrenaline, adrenaline):** HCT may reduce the response to pressor amines such as noradrenaline; clinical significance of this effect is uncertain and not sufficient to preclude their use.
- **HCT and Vitamin D and calcium salts:** May potentiate the rise in serum calcium. May lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyridism, malignancy or Vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.
- **HCT and Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren:** 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.

FERTILITY, PREGNANCY AND LACTATION:
Fertility: There is no clinical studies on fertility with amlodipine/valsartan/hydrochlorothiazide.
Pregnancy: Pregnancy Category D: Not recommended during first trimester and contraindicated during the second and third trimester of pregnancy.
Lactation: Amlodipine and hydrochlorothiazide is excreted in human milk. Use of this medicinal product during breast-feeding is not recommended.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking medicinal products containing amlodipine suffer from dizziness, headache, fatigue or nausea, the ability to react may be impaired.

UNDESIRABLE EFFECTS: The following additional adverse reactions have been reported in post marketing experience:
Amlodipine: With amlodipine, gynecomastia has been reported infrequently and a causal relationship is uncertain. Jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis), in some cases severe enough to require hospitalization, have been reported in association with use of amlodipine.
Valsartan or valsartan/hydrochlorothiazide: The following additional adverse reactions have been reported in post-marketing experience with valsartan or valsartan/hydrochlorothiazide:
- **Blood and Lymphatic:** Decrease in haemoglobin, decrease in haematocrit, neutropenia
- **Hypersensitivity:** There are rare reports of angioedema. Some of these patients previously experience angioedema with other drugs including ACE inhibitors, **Onato®-V HCT** should not be re-administered to patients who have had angioedema.
- **Digestive:** Elevated liver enzymes and very rare reports of hepatitis
- **Clinical Laboratory Tests:** Hyperkalaemia
- **Vascular:** Vasculitis
- **Renal:** Impaired renal function, renal failure
- **Dermatologic:** Alopecia
- **Nervous System:** Syncope
- Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide: The following additional adverse reactions have been reported in post-marketing experience with hydrochlorothiazide:
- Acute renal failure, renal disorder, aplastic anaemia, erythema multiforme, pyrexia, muscle spasm, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control, hypokalaemia, blood lipids increased, hyponatraemia, hypomagnesaemia, hypercalcaemia, hypochloraemic alkalosis, impotence, visual impairment.
- Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic evaluation is necessary

OVERDOSE:
Amlodipine: 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. Amlodipine is unlikely to be removed by haemodialysis. Valsartan: Valsartan is unlikely to be removed by haemodialysis.
Hydrochlorothiazide: Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II antagonists, other combinations, **ATC code:** C09DX01.

MECHANISM OF ACTION: Amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.
Amlodipine Mechanism of action: Amlodipine inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the anti-hypertensive 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 Mechanism of action: 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.
Hydrochlorothiazide Mechanism of action: The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. A high-affinity receptor in the renal cortex is the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly, by this diuretic action, reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

PHARMACOKINETIC PROPERTIES:
Amlodipine Absorption, Distribution, Biotransformation, Elimination: Peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Volume of distribution is approximately 21 l/kg. Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites. 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. 10% of original amlodipine and 60% of amlodipine metabolites are excreted in urine.
Valsartan Absorption Distribution Biotransformation, Elimination: Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability is 23%. 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. Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. 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.
Hydrochlorothiazide Absorption, Distribution, Biotransformation, Elimination: The absorption of hydrochlorothiazide, after an oral dose, is rapid (Tmax about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range. The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration. The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma. Hydrochlorothiazide is eliminated predominantly as unchanged compound.

SHELF LIFE:
See expiry on the pack.

AVAILABILITY
Onato®-V HCT tablet 5mg/160mg/12.5mg in a pack of 28's
Onato®-V HCT tablet 5mg/160mg/25mg in a pack of 28's
Onato®-V HCT tablet 10mg/160mg/12.5mg in a pack of 28's
Onato®-V HCT tablet 10mg/160mg/25mg in a pack of 28's
Onato®-V HCT tablet 10mg/320mg/25mg in a pack of 14's

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

Full Prescribing Information available on www.samipharmapk.com

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

اُناٹو-وی ایچ سی ٹی ٹیبلٹ
(ایملوڈیپین بیسیلیٹ + والسارٹن + ہائیڈروکلوروتھائیزائیڈ)

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۔

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