AMLOWELL™
(Amlodipine + Valsartan)

ایملو ویل

QUALITATIVE AND QUANTITATIVE COMPOSITION
AMLOWELL 5 mg+80 mg Tablets
Each film-coated tablet contains:
Amlodipine Besylate USP equivalent to Amlodipine..... 5 mg
Valsartan USP..... 80 mg
AMLOWELL 5 mg+160 mg Tablets
Each film-coated tablet contains:
Amlodipine Besylate USP equivalent to Amlodipine..... 5 mg
Valsartan USP..... 160 mg
AMLOWELL 10 mg+160 mg Tablets
Each film-coated tablet contains:
Amlodipine Besylate USP equivalent to Amlodipine..... 10 mg
Valsartan USP..... 160 mg

DESCRIPTION
AMLOWELL is a combination product containing Amlodipine + Valsartan. AMLOWELL contains the besylate salt of Amlodipine, a dihydropyridine calcium-channel blocker (CCB). Valsartan is a non-peptide, orally active, and specific angiotensin II receptor blocker acting on the AT1 receptor subtype used as an antihypertensive agent. Its chemical name is N-(1-oxopentyl)- N-[[2'-(1H -tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]- L-valine. The molecular formula is $C_{24}H_{29}N_5O_3$. Amlodipine besylate's chemical name is 3- Ethyl-5 -methyl (4RS)- 2- [(2-aminoethoxy) methyl] -4 -(2 chlorophenyl)- 6-methyl-1, 4-dihydropyridine- 3,5- dicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$

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

CLINICAL INFORMATION
Indications
Hypertension
AMLOWELL (Amlodipine + Valsartan) is indicated for the treatment of hypertension in adults:
• In patients not adequately controlled on monotherapy
• As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals
Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.

Dosage and Administration
The recommended dosage of AMLOWELL (Amlodipine + Valsartan) is one tablet per day. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of 10 mg + 320 mg once daily. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose.
The usual starting dose of AMLOWELL 5 mg+160 mg tablet once daily in patients who are not volume-depleted.

AMLOWELL 5 mg+80 mg may be administered in patients whose blood pressure is not adequately controlled with Amlodipine 5 mg or Valsartan 80 mg alone.
AMLOWELL 5 mg+160 mg may be administered in patients whose blood pressure is not adequately controlled with Amlodipine 5 mg or Valsartan 160 mg alone.

AMLOWELL 10 mg+160 mg may be administered in patients whose blood pressure is not adequately controlled with Amlodipine 10 mg or Valsartan 160 mg alone or with AMLOWELL 5 mg+160 mg.

For convenience, patients receiving Amlodipine + Valsartan from separate dosage forms may be switched to AMLOWELL tablets containing the same component doses.
Dosage adjustment
Renal Impairment
Safety and effectiveness of Valsartan+Amlodipine in patients with severe renal impairment (CrCl < 30 mL/min) have not been established. No dose adjustment is required in patients with mild (CrCl 60 to 90 mL/min) to moderate (CrCl 30 to 60 mL/min) renal impairment.
Hepatic Impairment
Amlodipine + Valsartan is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Exposure to Amlodipine is increased in patients with hepatic insufficiency. Limited data is available to suggest initial dose of 2.5 mg of Amlodipine in patients with all levels of hepatic impairment, which is not an available strength with AMLOWELL. When switching eligible hypertensive patients with hepatic impairment to Amlodipine + Valsartan combination, the strength with the lowest available dose of Amlodipine component 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 AMLOWELL, the strength with the lowest available dose of the Amlodipine component should be used.
Pediatric population
The safety and efficacy of AMLOWELL in children aged below 18 years have not been established. No data are available.

Administration Requirements
AMLOWELL can be administered orally as a single dose at any time of day, with or without food. The tablet should be swallowed whole. AMLOWELL may be administered with other antihypertensive agents.

Contraindications
• Known hypersensitivity to the active substances Valsartan or any of the dihydropyridine derivatives including Amlodipine.
• Severe hepatic impairment, biliary cirrhosis or cholestasis.
• Do not Co-administer Amlodipine + Valsartan combination with aliskiren or aliskiren-containing products in patients with diabetes mellitus or renal impairment (CrCl <60 ml/min)
• 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)
• Hemodynamically unstable heart failure after acute myocardial infarction

Warnings and Precautions
Fetal Toxicity
Amlodipine + Valsartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Amlodipine + Valsartan as soon as possible
Hypotension
In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur with angiotensin receptor blockers. Volume depletion should be corrected prior to administration of

Amlodipine + Valsartan and treatment should begin under close medical supervision.

Therapy with Amlodipine + Valsartan should also be initiated with caution in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis. Patients with heart failure or post-myocardial infarction patients given Valsartan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed.

Since the vasodilation induced by Amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution, as with any other peripheral vasodilator, should be exercised when administering Amlodipine, particularly in patients with severe aortic stenosis.

If excessive hypotension occurs with Amlodipine + Valsartan, the patient should be placed in a supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has been stabilized.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE inhibitors and ARBs should not be used concomitantly in patients with diabetic nephropathy.

Impaired renal function

Changes in renal function including acute renal failure can be caused by drugs that inhibit the renin-angiotensin system and by diuretics. Patients whose renal function may depend in part on the activity of the renin angiotensin system (e.g., patients with renal artery stenosis, chronic kidney disease, severe congestive heart failure, or volume depletion) may be at particular risk of developing acute renal failure on Amlodipine + Valsartan. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on Amlodipine + Valsartan therapy. No dose adjustment is required in patients with existing mild (CrCl 60 to 90 mL/min) to moderate (CrCl 30 to 60 mL/min) renal impairment. Monitoring of potassium levels and creatinine is advised in moderate renal impairment. Safety and effectiveness of Valsartan+Amlodipine in patients with severe renal impairment (CrCl < 30 mL/min) have not been established.

Renal artery stenosis

Amlodipine + 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 + Valsartan in patients who have had recent kidney transplantation.

Hepatic Impairment

Valsartan is mostly eliminated unchanged via the bile. The half-life of Amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Valsartan+Amlodipine is contraindicated in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Caution should be exercised when administering Amlodipine + Valsartan combination product to patients with mild to moderate hepatic impairment.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonists such as 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 drugs, including ACE inhibitors. AMLOWELL should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Risk of Myocardial Infarction or Increased Angina

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is required with use of Amlodipine + Valsartan in patients suffering from mitral stenosis or significant aortic stenosis or obstructive hypertrophic cardiomyopathy.

Interactions

No drug interaction studies have been conducted with Valsartan + Amlodipine combination product, although studies are available with the individual components, Valsartan + Amlodipine.

Amlodipine

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 for hypotension and edema is advised and dose adjustment may be required.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers (e.g. *anticonvulsant agents [carbamazepine, phenobarbital, phenytoin, fosphenytoin, and primidone], rifampicin, Hypericum perforatum)* on Amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of Amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Sildenafil

Monitor for hypotension when sildenafil is co-administered with Amlodipine due to additive effects on blood pressure lowering.

Simvastatin

Co-administration of simvastatin with Amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on Amlodipine to 20 mg daily.

Immuno Suppressants

Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and dose should be adjusted when appropriate.

Intravenous Dantrolene

Lethal ventricular fibrillation and cardiovascular collapse have been observed along with hyperkalemia after administration of verapamil and intravenous dantrolene, in animals. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as Amlodipine should be avoided with intravenous dantrolene in patients with malignant hyperthermia.

Grape Fruit 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.

Valsartan

Non-Steroidal Anti-Inflammatory Drugs and Selective COX-2 inhibitors

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including Valsartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving Valsartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including Valsartan, may also be attenuated by NSAIDs including selective COX-2 inhibitors.

Potassium Supplements and Drugs Causing Hyperkalemia

Concomitant use of Valsartan with other agents that block the renin-angiotensin system, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium or other drugs that may increase potassium levels (e.g., heparin) may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co-medication is considered necessary, monitoring of serum potassium is advised.

Drugs that are Inhibitors of Hepatic Uptake Transporter or Hepatic Efflux Transporter

Valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to Valsartan.

Lithium

Increases in serum lithium concentrations and lithium toxicity may occur during concomitant administration of lithium with angiotensin II receptor antagonists, including Valsartan. Monitor serum lithium levels during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with AMLOWELL.

Drugs causing Dual Blockade of the Renin Angiotensin Aldosterone System (RAAS)

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, hyperkalemia and decreased renal function (including acute renal failure).

Pregnancy and Breastfeeding

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

US FDA Pregnancy category D

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.

No information is available regarding the use of AMLOWELL during breast feeding, therefore AMLOWELL is not recommended and alternative treatments with better established safety profiles during breast feeding are preferable, especially while nursing a newborn or preterm infant.

Effects on ability to drive and use machines

Patients taking Amlodipine + 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.

Adverse reactions

The adverse reactions that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Amlodipine + Valsartan but at a higher incidence in Amlodipine + Valsartan patients (n=1437) than placebo (n=337) included peripheral edema (5.4% vs 3.0%), nasopharyngitis (4.3% vs 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

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: The following additional adverse reactions have been reported in postmarketing experience with Valsartan:

Hypersensitivity: Angioedema has been reported. Some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Valsartan should not be re-administered to patients who have had angioedema.

Digestive: Elevated liver enzymes and reports of hepatitis

***Musculoskeletal*:** Rhabdomyolysis

Renal: Impaired renal function, renal failure

Dermatologic: Alopecia, bullous dermatitis

Blood and Lymphatic: Thrombocytopenia

Vascular: Vasculitis

Overdose

Amlodipine

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. In humans, experience with intentional overdosage of Amlodipine is limited. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As Amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. 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.

Valsartan

Limited data are available related to overdosage in humans. The most likely effect of overdose with Valsartan would be peripheral vasodilation, hypotension, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse, and shock have been reported. If symptomatic hypotension should occur institute supportive treatment.

Valsartan is not removed from the plasma by hemodialysis.

PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Amlodipine + Valsartan combination with complementary mechanisms to control blood pressure in patients with essential hypertension.

Amlodipine

Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine binds to both dihydropyridine and non dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a

reduction in peripheral vascular resistance and reduction in blood pressure.

Valsartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland thus contributing to the antihypertensive effects. Its action is therefore independent of the pathways for angiotensin II synthesis.

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.

Pharmacokinetic Properties

Valsartan and Amlodipine exhibit linear pharmacokinetics.

Amlodipine + Valsartan combination

Following oral administration of Amlodipine + Valsartan in normal healthy adults, peak plasma concentrations of Amlodipine + Valsartan are reached in 3 and 6 to 8 hours, respectively. The rate and extent of absorption of Amlodipine + Valsartan from the combination tablet were the same as when administered as individual tablets. The bio-availabilities of Amlodipine + Valsartan are not altered by the co-administration of food.

Amlodipine

Absorption

After oral administration of therapeutic doses of Amlodipine alone, peak plasma concentrations of Amlodipine are reached in 6–12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution

Volume of distribution is approximately 21 l/kg. *In vitro* studies with Amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Metabolism

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%, although from about 8 h post dosing plasma Valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and Valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of Valsartan after intravenous administration is about 17 litres, indicating that Valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism

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 ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated in feces (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.

PHARMACEUTICAL INFORMATION

Shelf life

2 years

Special Precautions for Storage

Do not store above 30˚C.
Keep out of the reach of children.
Protect from light and moisture.

ہدایات:
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔ دوا کو روشنی اور نمی سے بچائیں۔

Nature and Contents of Container

AMLOWELL (Amlodipine+Valsartan) 5 mg + 80 mg tablets are available in a blister pack of 14's (2x7's).
AMLOWELL (Amlodipine+Valsartan) 5 mg + 160 mg tablets are available in a blister pack of 14's (2x7's).
AMLOWELL (Amlodipine+Valsartan) 10 mg + 160 mg tablets are available in a blister pack of 14's (2x7's).

MANUFACTURED BY

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