xxxxxxxxx-5343

VALSARTAN + AMLODIPINE BESILATE

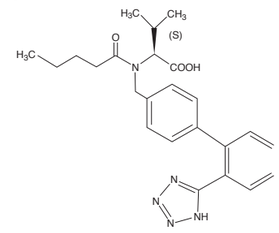
AMLOVAL 80/5
AMLOVAL 160/5
AMLOVAL 160/10

80 mg / 5 mg Film-Coated Tablet
160 mg / 5 mg Film-Coated Tablet
160 mg / 10 mg Film-Coated Tablet
ANTIHYPERTENSIVE

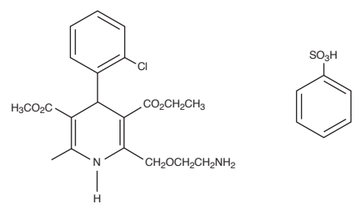
FORMULATION:
Each film-coated tablet contains:
Valsartan…… 160 mg / 80 mg
Amlodipine Besilate equivalent to
Amlodipine …….. 10 mg / 5 mg

PRODUCT DESCRIPTION:
Valsartan + Amlodipine Besilate (Amloval 160/10) 160 mg / 10 mg Film-Coated Tablet is a light peach colored, oval shaped, beveled edge, biconvex film-coated tablet with breakline on both side.
Valsartan + Amlodipine Besilate (Amloval 160/5) 160 mg / 5 mg Film-Coated Tablet is a yellow to dark yellow colored, oval shaped, beveled edge, biconvex film-coated tablet debossed with "1072" on one side and plain on other side.
Valsartan + Amlodipine Besilate (Amloval 80/5) 80 mg / 5 mg Film-Coated Tablet is a yellow to dark yellow colored, oval shaped, beveled edge, biconvex film-coated tablet debossed with "1071" on one side and plain on other side.

DESCRIPTION:
Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Valsartan's chemical name is N (1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4- yl]methyl]-L-valine; its structural formula is:



Its empirical formula is $C_{24}H_{29}N_5O_3$ and its molecular weight is 435.5.
Amlodipine besilate is the besilate salt of amlodipine, a dihydropyridine calcium channel blocker (CCB). It is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Amlodipine besilate'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 structural formula is:



Its empirical formula is $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$ and its molecular weight is 567.1.

PHARMACODYNAMICS:
This fixed dose combination combines two antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: Valsartan belongs to the angiotensin II antagonist class and amlodipine to the calcium antagonist class of medicines.

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. The increased plasma levels of angiotensin II following AT1 receptor blockade with valsartan may stimulate the unblocked receptor subtype AT2, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor.
Valsartan does not inhibit ACE, also known as kininase II, which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing.
Administration of valsartan to patients with hypertension results in a drop in blood pressure without affecting pulse rate.
In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak drop in blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Amlodipine
The amlodipine component of this fixed dose combination 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. 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.
Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.
Plasma concentrations correlate with effect in both young and elderly patients.
In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.
As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.
Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

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

PHARMACOKINETICS:

Valsartan:
Valsartan is rapidly absorbed following oral administration, with a bioavailability of about 23%. Peak plasma concentrations of valsartan occur 2 to 4 hours after an oral dose. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolized and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 5 to 9 hours. Following an oral dose about 83% is excreted in the feces and 13% in urine.

Amlodipine:
Amlodipine is well absorbed following oral administration with peak blood concentrations occurring after 6 to 12 hours. The bioavailability varies but is usually about 60 to 65%. Amlodipine is reported to be about 97.5% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of administration. Amlodipine is extensively metabolized in the liver; metabolites are mostly excreted in urine together with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

INDICATION:
Treatment of essential hypertension.
It is indicated in patients whose blood pressure is not adequately controlled on valsartan or amlodipine monotherapy.

DOSAGE AND ADMINISTRATION:
The recommended dose is one tablet per day.
Valsartan + Amlodipine may be administered in patients whose blood pressure is not adequately controlled with valsartan or amlodipine alone.
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 valsartan + amlodipine tablet containing the same component doses.

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
Caution should be exercised when administering to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan.

Elderly (age 65 years or over)
In elderly patients, caution is required when increasing the dosage.

Children and adolescents
Fixed dose combination of valsartan and amlodipine tablet is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Method of Administration:
It can be used with or without food. It is recommended to be taken with some water.

CONTRAINDICATIONS:
*Hypersensitivity to the active substances, to dihydropyridine derivatives, or to any of the excipients.
*Severe hepatic impairment, biliary cirrhosis or cholestasis
*Severe renal impairment (GFR<30 mL/min/1.73 m2) and patients undergoing dialysis.
*Second and third trimesters of pregnancy.

WARNINGS & PRECAUTIONS:

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 or close medical supervision at the start of treatment is recommended. If hypotension occurs with fixed dose combination of valsartan and amlodipine tablet, 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
No data are available in patients with bilateral renal artery stenosis or stenosis to a solitary kidney.

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

Hepatic impairment
Valsartan is mostly eliminated unchanged via the bile, whereas amlodipine is extensively metabolised by the liver. Particular caution should be exercised when administering it 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 is required for patients with mild to moderate renal impairment (GFR>30 ml/min/1.73 m2). 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.

Heart failure
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 angiotensin-converting enzyme (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.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

DRUG INTERACTIONS:
Interactions linked to valsartan
Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported in literature during concurrent use of ACE inhibitors. Despite the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

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 drugs (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid (>3 g/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.

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.

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

Caution required with concomitant use

CYP3A4 inhibitors
Diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increases by approximately 50% and the effect of amlodipine is increased). The possibility that more potent inhibitors of CYP3A4 (i.e. ketoconazole, itraconazole, ritonavir) may increase the plasma concentration of amlodipine to a greater extent than diltiazem cannot be excluded.

CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum [St. John's Wort]).
Co-administration may lead to reduced plasma concentrations of amlodipine. Clinical monitoring is indicated, with possible dosage adjustment of amlodipine during the treatment with the inducer and after its withdrawal.

To be taken into account with concomitant use

Others
In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, antacid medicines (aluminum hydroxide gel, magnesium hydroxide, simeticone), cimetidine, non-steroidal anti-inflammatory drugs, antibiotics and oral hypoglycemic drugs.

PREGNANCY AND LACTATION:
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.
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Antagonists (AIIRAs), similar risks may exist for this class of drugs. 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.

Lactation
It is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

ADVERSE REACTIONS:
Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000, including isolated reports).

Infections and infestations	
Common:	Nasopharyngitis, influenza
Immune system disorders	
Rare:	Hypersensitivity
Psychiatric disorders	
Rare:	Anxiety
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, somnolence, dizziness postural, paraesthesia
Eye disorders	
Rare:	Visual disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Rare:	Tinnitus
Cardiac disorders	
Uncommon:	Tachycardia
Rare:	Syncope
Vascular disorders	
Uncommon:	Orthostatic hypotension
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Cough, pharyngolaryngeal pain
Gastrointestinal disorders	
Uncommon:	Diarrhea, nausea, abdominal pain, constipation, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Rash, erythema
Rare:	Hyperhidrosis, exanthema, pruritus
Musculoskeletal and connective tissue disorders	
Uncommon:	Joint swelling, back pain, arthralgia
Rare:	Muscle spasm, sensation of heaviness
Renal and urinary disorders	
Rare:	Pollakiuria, polyuria
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
General disorders and administration site conditions	
Common:	Edema, pitting edema, facial edema, edema peripheral, fatigue, flushing, asthenia, hot flush

Additional information on the combination
Peripheral edema, a recognized adverse effect of amlodipine, was generally observed at a lower incidence in patients who received the amlodipine/valsartan combination than in those who received amlodipine alone.

Additional information on the individual components

Valsartan
Not known Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia, increase of serum potassium, elevation of liver function values including increase of serum bilirubin, renal failure and impairment, elevation of serum creatinine, angioedema, myalgia, vasculitis, hypersensitivity including serum sickness.

Amlodipine
Common: Vomiting.
Uncommon: Alopecia, altered bowel habits, dyspepsia, dyspnoea, rhinitis, gastritis, gingival hyperplasia, gynaecomastia, hyperglycaemia, impotence, increased urinary frequency, leucopenia, malaise, mood changes, myalgia, peripheral neuropathy, pancreatitis, hepatitis, thrombocytopenia, vasculitis, angioedema and erythema multiforme.
Rare : Arrhythmia, myocardial infarction. Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed increased frequency, duration or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. Arrhythmia (including ventricular tachycardia and atrial fibrillation) has also been reported. These adverse events may not be distinguishable from the natural history of the underlying disease.
Very rare : Cholestatic jaundice, AST and ALT increase, purpura, rash and pruritus. Exceptional cases of extrapyramidal syndrome have been reported.

"For suspected adverse drug reaction, report to FDA: www.fda.gov.ph or to TORRENT: www.torrentpharma.com".
Patient to seek medical attention immediately at the first sign of any adverse drug reaction shall appear.

OVERDOSAGE AND TREATMENT:

Symptoms
There is no experience of overdose with valsartan/amlodipine tablet. 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 up to and including shock with fatal outcome have been reported.

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 valsartan/amlodipine tablet 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.

STORAGE AND CONDITION:
Store at temperatures not exceeding 30°C.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:
Valsartan+Amlodipine (Amloval 160/10) 160 mg /10 mg Film-Coated Tablet - Opa/Alu/PVC-Alu Blister pack of 10's (Box of 30's) - DRP -
Valsartan+Amlodipine (Amloval 160/5) 160 mg /5 mg Film-Coated Tablet - Opa/Alu/PVC-Alu Blister pack of 10's (Box of 30's) - DRP -
Valsartan+Amlodipine (Amloval 80/5) 80 mg /5 mg Film-Coated Tablet - Opa/Alu/PVC-Alu Blister pack of 10's (Box of 30's) - DRP -

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torrent PHARMA

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Makati City, PHILIPPINES

PRODUCT NAME	: Amloval	COUNTRY : Philippines	LOCATION : Indrad	Supersedes A/W No.:			
ITEM / PACK	: Insert	NO. OF COLORS: 1	REMARK :				
DESIGN STYLE	: Front-Back	PANTONE SHADE NOS.:	SUBSTRATE :				
CODE	: xxxxxxxxx-5343	Black	Activities	Department	Name	Signature	Date
DIMENSIONS (MM)	: 150 x 470		Prepared By	Pkg.Dev			
ART WORK SIZE	: S/S		Reviewed By	Pkg.Dev			
DATE	: 13-07-2016		Approved By	Quality			

This colour proof is not colour binding. Follow Pantone shade reference for actual colour matching.