# Triforge™

(Amlodipine + Valsartan + Hydrochlorothiazide)

Highnoon

**COMPOSITION**
**Triforge 5mg/160mg/12.5mg Tablet:**
Each film-coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 160mg
Hydrochlorothiazide 12.5mg
**Triforge 5mg/160mg/25mg Tablet:**
Each film-coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 160mg
Hydrochlorothiazide 25mg
**Triforge 10mg/160mg/12.5mg Tablet:**
Each film-coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 160mg
Hydrochlorothiazide 12.5mg
**Triforge 10mg/160mg/25mg Tablet:**
Each film-coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 160mg
Hydrochlorothiazide 25mg
**Triforge 10mg/320mg/25mg Tablet:**
Each film-coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 320mg
Hydrochlorothiazide 25mg

**Mechanism of Action**
The active ingredients target three separate mechanisms involved in blood pressure regulation. Specifically, amlodipine blocks the contractile effects of calcium on cardiac and vascular smooth muscle cells; valsartan blocks the vasoconstrictiotn and sodium retaining effects of angiotensin II on cardiac, vascular smooth muscle, adrenal and renal cells; and hydrochlorothiazide directly promotes the excretion of sodium and chloride in the kidney leading to reductions in intravascular volume.

***Amlodipine***
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It binds to both dihydropyridine and nondihydropyridine 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. Its action is therefore independent of the pathways for angiotensin II synthesis.
There is also an $AT_2$ receptor found in many tissues, but $AT_2$ is not known to be associated with cardiovascular homeostasis.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

***Hydrochlorothiazide***
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.
The mechanism of the antihypertensive effect of thiazides is unknown.

**PHARMACOKINETICS**
Following oral administration in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and Hydrochlorothiazide are reached in about 6 hours, 3 hours, and 5 hours, respectively.
It may be administered with or without food.

***Amlodipine***
Amlodipine is well absorbed after oral doses and peak blood plasma concentrations occur after 6-12 hours, after administration of amlodipine alone. The bioavailability varies but is usually about 60% to 65%. Amlodipine is reported to be about 98% bound to plasma proteins. It has a prolonged terminal elimination half-life of 35 – 50 hours and steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing. Amlodipine is extensively metabolized in the liver; metabolites are mostly excreted in the urine; with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.

***Valsartan***
Valsartan is rapidly absorbed after oral dose with a bioavailability of about 25% when given as a tablet. Peak plasma concentration of valsartan tablet occurs in 2 to 4 hours. 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 6 hours. Following an oral dose about 83% is excreted in the feces and 13% in the urine.

***Hydrochlorothiazide***
Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine, hydrochlorothiazide crosses the placental barrier and is distributed into breast milk. Hydrochlorothiazide binds to albumin (65 to 70%).

**INDICATIONS AND USAGE**
- It is indicated for the treatment of hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes, and myocardial infarctions.
- It is not indicated for the initial therapy of hypertension.

**DOSAGE AND ADMINISTRATION**
- Dose once-daily. The dosage may be increased after 2 weeks of therapy. The full blood pressure lowering effect maybe achieved 2 weeks after being on the maximal dose of it. The maximum recommended dose is 10mg/320mg/25mg.
- It may be used as add on therapy for patients not adequately controlled on any 2 of the following antihypertensive classes: calcium channel blockers, angiotensin receptor blockers, and diuretics.
- A patient who experiences dose-limiting adverse reactions to an individual component while on any dual combination of the components of it; may be switched containing a lower dose of that component to achieve similar blood pressure reductions.
- It may be substituted as replacement therapy for the individually titrated components.
- It may be administered with other antihypertensive agents.
- In adult the initial dose of valsartan is 80mg once daily, increase if necessary up to 320 mg daily, dose to be increased at 4 weeks interval.
- In adult the initial dose of amlodipine is 5mg once daily, maximum 10mg per day.

**CONTRAINDICATIONS**
- Do not use in patients with anuria, hypersensitivity to other sulfonamide - derived drugs or hypersensitivity to any component of this product.
- Do not co-administer aliskiren with this product in patients with diabetes.
- Valsartan is contraindicated in biliary cirrhosis and cholestasis.
- Amlodipine is contraindicated in cardiogenic shock, significant aortic stenosis and unstable angina.

**WARNINGS AND PRECAUTIONS**
- It can cause fetal harm when administered to pregnant women. 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 it as soon as possible.
- Thiazides cross the placenta, and use of thiazides during pregnancy is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.
- 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.
- 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 this product. Monitor renal function periodically in these patients. Consider withholding or discontinuing therapy in patients who develop a clinically significant decrease in renal function on it.
- Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
- Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Increase in serum lithium concentrations and lithium toxicity have been reported with concomitant use of valsartan or thiazide diuretics. Monitor lithium levels in patients receiving this product and lithium.
- Some patients with heart failure develop increase in potassium with valsartan. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. Hydrochlorothiazide can cause hypokalemia and hyponatremia. Hypomagnesemia can result in hypokalemia which appears difficult to treat despite potassium repletion. Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), it should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides.
- Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.
- Hydrochlorothiazide may alter glucose tolerance and raise serum levels of cholesterol and triglycerides. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients. Hydrochlorothiazide decreases urinary calcium excretion and may cause elevations of serum calcium. Monitor calcium levels in patients with hypercalcemia receiving this product.
- It has not been studied in patients with heart failure, recent myocardial infarction, or 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. Do not initiate treatment in patients with aortic or mitral stenosis or obstructive hypertrophic cardiomyopathy. If excessive hypotension occurs with this product, place the patient in a supine position and, if necessary, give intravenous 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 stabilized.

**ADVERSE REACTIONS**
The reported adverse events associated with combine dose of valsartan, amlodipine hydrochlorothiazide are: dizziness, hypotension, oedema, headache dyspepsia, muscle spasm, back pain, nausea, nasopharyngitis, orthostatic postural dizziness, increase serum creatinine, increase blood urea nitrogen and neutropenia.
The reported adverse events associated with valsartan are: headache, dizziness, hypotension, upper respiratory infection, cough, arthralgia, fatigue, pruritus, rash, dry mouth, back pain, myalgia, hepatitis, elevated liver enzyme, syncope, hyperkalemia, liver transaminase elevations, impaired renal function, renal failure, alopecia, bullous dermatitis, vasculitis, neutropenia, rhabdomyolysis, angioedema, gastrointestinal disturbance, decrease hemoglobin and decrease hematocrit.

The reported adverse events associated with amlodipine are: gynecomastia, jaundice, hepatic enzyme elevations, dizziness, flushing, headache, hypotension, peripheral oedema, tachycardia, palpitations, nausea, constipation and other gastrointestinal disturbances, micturition disorder including increase frequency, lethargy, eye pain, visual disturbances, syncope, vertigo, migraine, mood disturbances, paradoxical increase in ischemic chest pain, excessive fall in blood pressure, cerebral or myocardial ischemia or transient blindness, rashes (including erythema multiforme), fever, abnormalities in liver function (including cholestasis), gingival hyperplasia, pruritus, myalgia, tremor, dry mouth, depression, hyperhidrosis, insomnia, malaise, pain, rhinitis, abnormal sensation, altered taste, altered, tinnitus, urinary disorder, weight gain, angioedema, confusion, leucopenia, hypersensitivity, muscle tone increased, pancreatitis, photosensitivity reactions, Stevens-Johnson Syndrome, thrombocytopenia, vasculitis, pulmonary oedema and impotence. Bradycardia, hyperglycemia, metabolic acidosis and coma may be associated with overdosage.

The adverse event associated with hydrochlorothiazide are: glycosuria, hyperglycemia, hyperuricemia, hypercalcemia, electrolyte imbalance (including hyperchloremic alkalosis, hyponatremia and hypokalemia), hypomagnesemia, changes in plasma lipids, signs of electrolyte imbalance (including dry mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain, muscle cramps, seizures, oliguria, hypotension and gastrointestinal disturbance), anorexia, gastric irritation, nausea, vomiting, constipation, diarrhea, sialadenitis, headache, dizziness, photosensitivity reactions, orthostatic hypotension, paresthesia, impotence, visual impairment , yellow vision, hypersensitivity reactions (including rash, fever, pulmonary oedema, pneumonitis, anaphylaxis and toxic epidermal necrolysis), cholestatic jaundice, pancreatitis, cancers (non-melanoma skin cancer), blood dyscrasias (including thrombocytopenia, granulocytopenia, leucopenia, aplastic anemia and hemolytic anemia), interstitial ulceration, acute renal failure, renal disorder, erythema multiforme, pyrexia, asthenia, acute angle-closure glaucoma, bone marrow failure, worsening of diabetes control and hypokalemia. Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have also been observed.

**DRUG INTERACTIONS**
***Amlodipine***
*Impact of Other Drugs on Amlodipine*
- CYP3A Inhibitors: Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.
- CYP3A Inducers: No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers (e.g., rifampicin, St. John's Wort).
- Monitor for hypotension when sildenafil is co-administered with amlodipine.

*Impact of Amlodipine on Other Drugs*
- Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20mg daily.
- Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered with immunosuppressants. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate.

***Valsartan***
- 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 advisable.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration 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 be attenuated by NSAIDs including selective COX-2 inhibitors.
- Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Most patients receiving the combination of two RAS inhibitors do not obtain any additional benefit compared to monotherapy. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function and electrolytes in patients on Valsartan and other agents that affect the RAS.
- Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists or thiazide. Monitor serum lithium levels during concomitant use.
- Elevations in creatinine, decrease in hemoglobin & hematocrit, occasional elevation of liver chemistries, neutropenia, increase in serum potassium and blood urea nitrogen was observed in patients taking Valsartan. Proper monitoring and caution should be taken while using Valsartan.

***Hydrochlorothiazide***
- Dosage adjustment of the antidiabetic (oral and insulin) drug may be required when administered concurrently with thiazide diuretics.
- Concomitant treatment with cyclosporine may increase the risk of hyperuricemia and gout-type complications. When used concomitantly with carbamazepine it may lead to symptomatic hyponatremia.
- Staggering the dosage of hydrochlorothiazide and ion exchange resins (e.g., cholestyramine, colestipol) such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimize the interaction.
- When it is used with nonsteroidal anti-inflammatory (NSAIDs and COX-2 selective inhibitors) agents concomitantly, the patient should be observed closely to determine if the desired effect of diuretic is obtained.
- Diuretic agents increase the risk of lithium toxicity. Monitoring of serum lithium concentrations is recommended during concurrent use.

**USE IN SPECIFIC POPULATIONS**
**Pregnancy**
It 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 leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension fetal and neonatal morbidity and death. Published reports include cases of anhydramnios and oligohydramnios in pregnant women treated with valsartan. When pregnancy is detected, discontinue it as soon as possible.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Thiazides can cross the placenta, and concentrations reached in the umbilical vein approach those in the maternal plasma.
Hydrochlorothiazide, like other diuretics, can cause placental hypoperfusion. It accumulates in the amniotic fluid, with reported concentrations up to 19 times higher than in umbilical vein plasma. Use of thiazides during pregnancy is associated with a risk of fetal or neonatal jaundice or thrombocytopenia. Since they do not prevent or alter the course of EPH (Edema, Proteinuria, Hypertension), gestosis (preeclampsia), these drugs should not be used to treat hypertension in pregnant women. The use of Hydrochlorothiazide, for other indications (e.g., heart disease) in pregnancy should be avoided.

**Lactation**
Hydrochlorothiazide is present in human milk. Limited published studies report that amlodipine is present in human milk. Because of the potential for serious adverse reactions in breastfed infants, advise a nursing woman that breastfeeding is not recommended during treatment with it.

**Paediatric Use**
The safety and effectiveness in paediatric patients have not been established.

**Geriatric Use**
Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

**Renal Impairment**
Safety and effectiveness 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) or moderate (CrCl 30 to 60 mL/min) renal impairment.

**Hepatic Impairment**
Exposure to amlodipine is increased in patients with hepatic insufficiency. In valsartan no dose adjustment is necessary for patients with mild-to-moderate disease. No dosing recommendations can be provided for patients with severe liver disease. Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.

**OVERDOSAGE**
Limited data are available related to over dosage in humans. The most likely manifestations of over dosage would be hypotension and tachycardia, bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension occur, supportive treatment should be instituted.

*Amlodipine*
Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome have been reported. If massive overdose occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, initiate cardiovascular support including elevation of the extremities and the judicious administration of fluids. 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*
Depressed level of consciousness, circulatory collapse, and shock have been reported. Valsartan is not removed from the plasma by hemodialysis.

*Hydrochlorothiazide*
The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

**DOSAGE AND INSTRUCTIONS**
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

**PRESENTATION**
**Triforge 5mg/160mg/12.5mg Tablets:**
Alu. Alu. Blister Pack of 4 x 7's.
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# ٹرائی فورج™

(ایملو ڈِپین + والسرٹان + ہائیڈروکلوروتھائیذائیڈ)

**خوراک و ہدایات:**
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

**Manufactured by**
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