Biforge™

(Amlodipine + Valsartan)

Highnoon

COMPOSITION
Biforge 5mg/80mg Tablet: Each film-coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 80mg
Biforge 5mg/160mg Tablet: Each film-coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 160mg
Biforge 10mg/160mg Tablet: Each film-coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 160mg
Biforge 5mg/320mg Tablet: Each film-coated tablet contains:
Amlodipine (as besylate) 5mg
Valsartan 320mg
Biforge 10mg/320mg Tablet: Each film-coated tablet contains:
Amlodipine (as besylate) 10mg
Valsartan 320mg

DESCRIPTION
Biforge is a fixed combination of amlodipine and valsartan.
Amlodipine is a dihydropyridine calcium channel blocker.
Valsartan is an angiotensin II receptor antagonist (ARB).

MECHANISM OF ACTION
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 AT1 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 AT2 receptor found in many tissues, but AT2 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 catalysed 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.

Amlodipine
Amlodipine is a dihydropyridine calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. 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.

PHARMACOKINETICS
Valsartan
Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23% when given as a tablet and about 39% when given as a solution. Peak plasma concentrations of valsartan occur 2 to 4 hours after tablet and 1 to 2 hours after oral solution. 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% excreted in the faeces and 13% in the urine.

Amlodipine
Amlodipine is well absorbed after oral doses and peak blood concentration occur after 6 to 12 hour. 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 hours to 50 hours and steady-state plasma concentrations are not achieved until after 7 to 8 days of use. Amlodipine is extensively metabolized in the liver; metabolites are mostly excreted in urine, with less than 10% of a dose as unchanged drug. Amlodipine is not removed by dialysis.
Following oral administration of valsartan and amlodipine in normal healthy adults, peak plasma concentrations of valsartan and amlodipine are reached in 3 hours and 6 hours to 8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine are the same as when administered as individual tablets. The bioavailabilities of amlodipine and valsartan are not altered by the coadministration of food.

INDICATIONS AND USAGE
Hypertension
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 may be used in patients whose blood pressure is not adequately controlled on either monotherapy.
It may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals.
The choice of this combination (amlodipine and valsartan) as initial therapy for hypertension should be based on an assessment of potential benefits and risks including whether the patient is likely to tolerate the lowest dose of it.

DOSAGE AND ADMINISTRATION
General Considerations
Dosage is once daily. The dosage can be increased after 1 to 2 weeks of therapy to a maximum of one 10/320 mg tablet once daily as needed to control blood pressure. The majority of the antihypertensive effect is attained within 2 weeks after initiation of therapy or a change in dose. It may be administered with or without food. It may be administered with other antihypertensive agents.

Add-on Therapy
A patient whose blood pressure is not adequately controlled with amlodipine (or another dihydropyridine calcium-channel blocker) alone or with valsartan (or another angiotensin II receptor blocker) alone may be switched to combination therapy with (amlodipine and valsartan).
A patient who experiences dose-limiting adverse reactions on either component alone may be switched to combination (amlodipine and valsartan) containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. The clinical response to this combination (amlodipine and valsartan) should be subsequently evaluated and if blood pressure remains uncontrolled after 3 to 4 weeks of therapy, the dose may be titrated up to a maximum of 10mg/320mg.

Replacement Therapy
For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive this combination (amlodipine and valsartan) of the tablet containing the same component doses.

Initial Therapy
A patient may be initiated on this combination (amlodipine and valsartan) if it is unlikely that control of blood pressure would be achieved with a single agent. The usual starting dose is 5mg/160mg once daily in patients who are not volume-depleted.

CONTRAINDICATIONS
- Do not use in patients with known hypersensitivity to any component.
- Do not co-administer aliskiren with this combination (amlodipine and valsartan) in patients with diabetes.

WARNINGS AND PRECAUTIONS
Fetal Toxicity
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 (amlodipine and valsartan) as soon as possible.

Hypotension
Excessive hypotension was seen in patients with uncomplicated hypertension treated with (amlodipine and valsartan). 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 in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of it (amlodipine and valsartan), or treatment with this combination (amlodipine and valsartan) should start under close medical supervision.
Caution should be observed when initiating therapy 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.
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 the combination (amlodipine and 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 stabilized.
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.

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 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 valsartan.
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 it (amlodipine and 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 it (amlodipine and valsartan).

Hyperkalemia
Drugs that inhibit the renin-angiotensin system can cause hyperkalemia. Monitor serum electrolytes periodically. Some patients with heart failure have developed increase in potassium. 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 it (amlodipine and valsartan) may be required.

ADVERSE REACTIONS
The reported adverse events associated with combine dose of valsartan and amlodipine are: peripheral edema, vertigo, upper respiratory tract infection, dizziness, orthostatic events (orthostatic hypotension and postural dizziness), lymphadenopathy, palpitations, tachycardia, ear pain, diarrhoea, nausea, constipation, dyspepsia, abdominal pain, gastritis, vomiting, abdominal discomfort, abdominal distention, dry mouth, colitis, fatigue, chest pain, asthenia, pitting edema, pyrexia, edema, seasonal allergies, sinusitis, bronchitis, pharyngitis, gastroenteritis, nasopharyngitis, tonsillitis, pharyngotonsillitis, bronchitis acute, epicondylitis, joint sprain, limb injury, gout, non-insulin-dependent diabetes mellitus, hypercholesterolemia, arthralgia, back pain, muscle spasms, pain in extremity, myalgia, osteoarthritis, joint swelling, musculoskeletal chest pain, headache, sciatica, paresthesia, cervicobrachial syndrome, carpal tunnel syndrome, hypoesthesia, sinus headache, somnolence, insomnia, anxiety, depression, hematuria, nephrolithiasis, pollakiuria, erectile dysfunction, cough, pharyngolaryngeal pain, sinus congestion, dyspnea, epistaxis, productive cough, dysphonia, nasal congestion, pruritus, rash, hyperhidrosis, eczema, erythema, flushing, hot flush, exanthema, syncope, visual disturbance, hypersensitivity, tinnitus, impotence, hypotension, decrease in hemoglobin, decrease in hematocrit, neutropenia, angioedema, elevated liver enzymes, hepatitis, impaired renal function, renal failure, hyperkalemia, alopecia, bullous dermatitis, vasculitis and rare cases of rhabdomyolysis.
The reported adverse events associated with amlodipine are arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, postural hypotension, vasculitis, neuropathy peripheral, tremor, anorexia, dysphagia, pancreatitis, gingival hyperplasia, allergic reaction, hot flushes, malaise, rigors, weight gain, weight loss, arthrosis, muscle cramps, sexual dysfunction (male and female), nervousness, abnormal dreams, depersonalization, dyspnea, angioedema, erythema multiforme, rash erythematous, rash maculopapular, abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus, micturition frequency, micturition disorder, nocturia, sweating increased, hyperglycemia, thirst, leukopenia, purpura, thrombocytopenia, cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, gynecomastia jaundice, hepatic enzyme elevations and xerophthalmia.
The reported adverse events associated with valsartan are headache, dizziness, hypotension, upper respiratory infection, cough, diarrhoea, rhinitis, sinusitis, nausea, pharyngitis, edema, arthralgia, viral infection, fatigue, abdominal pain, allergic reaction, asthenia, palpitations, pruritus, rash, constipation, dry mouth, dyspepsia, flatulence, back pain, muscle cramps, myalgia, anxiety, insomnia, paraesthesia, hepatitis, somnolence, dyspnoea, vertigo, impotence, chest pain, syncope, anorexia, vomiting, angioedema, hyperkalemia, liver transaminase elevations, elevations in creatinine, elevations in serum potassium, impaired renal function, increases in blood urea nitrogen, renal failure, alopecia, bullous dermatitis, vasculitis, thrombocytopenia, neutropenia, rhabdomyolysis and blurred vision.

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.
- 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 20 mg daily.
- 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 adjust the dose when appropriate.

Valsartan
- Co-administration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time course of the anticoagulant properties of warfarin.
- CYP 450 Interactions: CYP 450 mediated drug interactions between valsartan and co-administered drugs are unlikely because of the low extent of metabolism.
- 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.
- 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.
- Do not co-administer aliskiren with valsartan in patients with diabetes. Avoid use of aliskiren with valsartan in patients with renal impairment (GFR <60 mL/min).
- Increase in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use.

USE IN SPECIFIC POPULATIONS
Pregnancy
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 tablet as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimesters of pregnancy. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.
There is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment. If oligohydramnios is observed, discontinue amlodipine and valsartan, unless it is considered life saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Closely observe infants with histories of in utero exposure to amlodipine and valsartan for hypotension, oliguria, and hyperkalemia.

Nursing Mothers
It is not known whether valsartan is excreted in human milk. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from amlodipine and valsartan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

Paediatric Use
Safety and effectiveness of amlodipine and valsartan in paediatric patients have not been established.

Geriatric Use
There were no notable differences in efficacy or safety between older and younger patients.

Amlodipine: In general, 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. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40% to 60%.

Valsartan: No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment
Safety and effectiveness of amlodipine and valsartan 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
Valsartan: No dose adjustment is necessary for patients with mild-to-moderate liver disease. No dosing recommendations can be provided for patients with severe liver disease.

Amlodipine: Exposure to amlodipine is increased in patients with hepatic insufficiency. The recommended initial dose of amlodipine in patients with hepatic impairment is 2.5 mg.

OVERDOSAGE
Valsartan
Limited data are available related to overdosage in humans. The most likely manifestations of overdosage 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, supportive treatment should be instituted. Valsartan is not removed from the plasma by hemodialysis.

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 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.

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 a dry place. Protect from light.

PRESENTATION
Biforge 5mg/80mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Biforge 5mg/160mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Biforge 10mg/160mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Biforge 5mg/320mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Biforge 10mg/320mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.

بائی فورج™

(ایملوڈپین + والسرٹان)

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
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14002583