Address Tablets*

ایڈریس ٹیبلٹس

COMPOSITION

Address 5/80 mg Tablets

Each film coated tablet contains:

Amlodipine (as besylate) BP / Valsartan BP ..... 5 /80 mg

Address 5/160 mg Tablets

Each film coated tablet contains:

Amlodipine (as besylate) BP / Valsartan BP ..... 5/160 mg

DESCRIPTION

Address (Amlodipine / Valsartan) is a fixed combination of two anti-hypertensives with complementary mechanisms to control blood pressure in patients with essential hypertension.

Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol. Chemically it is 3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine -3,5-dicarboxylate benzenesulphonate and its molecular weight is 567.1.

Valsartan is a white to practically white fine powder, soluble in ethanol and methanol and slightly soluble in water. Chemically it is N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1,1'-biphenyl]-4-yl] methyl]-L-valine and its molecular weight is 435.5.

PHARMACOLOGY

Mechanism of Action:

Amlodipine: It belongs to a therapeutic class called calcium channel blockers (CCBs). It blocks the transport of calcium into the smooth muscle cells lining the coronary arteries and other arteries of the body. Since calcium is important in promoting contraction of muscles, blocking calcium transport relaxes the muscles that surround arteries, dilating (enlarging) the arteries of the body including the arteries of the heart (coronary arteries). Dilating arteries lowers blood pressure.

Valsartan: It is an orally active, potent and specific angiotensin II (Ang II) receptor blocker (ARBs). Angiotensin is formed in the blood by the action of angiotensin converting enzyme (ACE) on a chemical in blood called angiotensinogen. It is a powerful chemical that attaches to angiotensin receptors found in many tissues but primarily on smooth muscle cells surrounding blood vessels. Its attachment to the receptors causes the blood vessels to narrow (constrict) which leads to an increase in blood pressure (hypertension). Valsartan blocks the angiotensin receptors. By blocking the action of angiotensin, valsartan dilates blood vessels and reduces blood pressure.

Pharmacokinetics:

Amlodipine:

Absorption: After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations (Cmax) of amlodipine are reached in 6-12 hours. Absolute bioavailability has been estimated to be between 64% and 80%. The bioavailability of amlodipine is unaffected by food ingestion.

Distribution: Volume of distribution of is approximately 21 L/kg. Approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation: Amlodipine is extensively (about 90%) metabolized in the liver to inactive metabolites.

Elimination: Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of about 30 to 50 hours. Steady state plasma levels are reached after continuous administration for 7 to 8 days. 10% 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 the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (Cmax) by about 50%, although from about 8 hours post dosing, plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given with or without food.

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

Biotransformation: Valsartan is not transformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (less than 10% of valsartan AUC). This metabolite is metabolically inactive.

Elimination: Valsartan shows multiexponential decay kinetics (t1/2 α <1h and t1/2 β about 9h). Valsartan is primarily eliminated unchanged in faeces (about 83% of dose) and urine (about 13% of dose) mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Address (Amlodipine / Valsartan):

Following oral administration of Address peak plasma concentrations of valsartan and amlodipine are reached in 3 and 6-8 hours, respectively. The rate and extent of absorption of valsartan and amlodipine from Address are equivalent to the bioavailability of amlodipine and valsartan when administered as individual tablets.

INDICATIONS

Treatment of essential hypertension.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients.
- Pregnancy and lactation.
- Concomitant use of ARBs - including valsartan – or of ACEIs with aliskiren in patients with Type 2 diabetes.

ADVERSE EFFECTS

Infections and infestations:

Common: Nasopharyngitis, influenza

Immune system disorders:

Rare: Hypersensitivity

Eye disorders:

Rare: Visual disturbance

Psychiatric disorders:

Rare: Anxiety

Nervous system disorders:

Common: Headache

Uncommon: Dizziness, somnolence, postural dizziness, paresthesia

Ear and labyrinth disorders:

Uncommon: Vertigo

Rare: Tinnitus

Cardiac disorders:

Uncommon: Tachycardia, palpitation

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: Oedema, pitting oedema, peripheral oedema, fatigue, flushing, asthenia, hot flush

Clinically Significant Adverse Reactions:**

Fulminant hepatitis & rhabdomyolysis

DRUG INTERACTIONS

Amlodipine:

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

CYP3A Inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypersensitive patients resulted in a 1.6-fold increase in amlodipine systemic exposure. However, strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Caution should therefore be exercised when co-administering amlodipine with CYP3A4 inhibitors.

Grapefruit Juice: The exposure of amlodipine may be increased when co-administered with grapefruit juice due to CYP3A4 inhibition.

CYP3A4 Inducers: No information is available on the quantitative effects of CYP3A4 inducers on amlodipine. Patients should be monitored for adequate clinical effect when amlodipine is co-administered with CYP3A4 inducers. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, combination of Aluminum hydroxide gel, Magnesium hydroxide and simethicone, cimetidine, non-steroidal anti-inflammatory drugs, antibiotic and oral hypoglycemic drugs.

Valsartan:

Dual blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren: The concomitant use of ARBs, including valsartan with other agents acting on the RAS is associated with an increased incidence of hypotension, hyperkalemia, and changes in renal function compared to monotherapy. It is recommended to monitor blood pressure, renal function and electrolytes in patients on Address and other agents that affect the RAS. The concomitant use of ARBs-including valsartan – or ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min).

The concomitant use of ARBs-including valsartan – or ACEIs with aliskiren is contraindicated in patients with Type 2 diabetes.

Potassium: Concomitant use of potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, etc.) requires caution and frequent monitoring of potassium levels.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 inhibitors (COX-2) inhibitors: When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonist and NSAIDs may lead to increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Lithium: Reversible increase in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACEIs or ARBs including Address. Therefore, careful monitoring of serum lithium levels is recommended during concomitant use. If a diuretic is also used, the risk of lithium toxicity may presumably be increased further with Address.

Transporters: Valsartan is a substitute of the hepatic uptake transporters OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (e.g. rifampin, ciclosporin) or efflux transporter (e.g. ritonavir) may increase the systemic exposure to valsartan.

In monotherapy with valsartan, no drug interactions of clinical significance have been found with the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

WARNINGS AND PRECAUTIONS

Patients with sodium and / or volume depletion:

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 of Address or close medical supervision at the start of treatment is recommended.

Hyperkalemia:

Concomitant use of potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium or other drugs that may increase potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.

Fetal/Neonatal morbidity and mortality:

Amlodipine and valsartan can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Drug that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. ACEIs use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction with use of valsartan during pregnancy. If pregnancy is detected during therapy, Address should be stopped immediately.

Patients with renal artery stenosis:

Address should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis, stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Patients with renal impairment:

No data is available for severe cases (creatinine clearance < 10 mL/min.) and caution is therefore advised. No dosage adjustment of Address is required for patients with mild to moderate renal impairment.

The use of ARBs-including valsartan-or of ACEIs with aliskiren should be avoided in patients with severe renal impairment (GFR < 30 mL/min).

Patients with kidney transplantation:

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

Patients with hepatic impairment:

Valsartan is mostly eliminated unchanged via the bile whereas amlodipine is extensively metabolized by the liver. Particular caution should be exercised when administering Address to patients with hepatic impairment or biliary obstructive disorders.

Angioedema:

Address should be immediately discontinued in patients who develop angioedema, and Address should not be re-administered.

Patients with heart failure/post-myocardial infarction:

In general, CCBs including amlodipine should be used with caution in patients with serious congestive heart failure.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with ACEIs or ARBs has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death.

Patients with acute myocardial infarction:

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

Patients with aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

As with all other vasodilators, special caution is required when using amlodipine in patients suffering from aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Dual Blockade of the Renin-Angiotensin System (RAS):

Caution is required while co-administering ARBs, including valsartan, with other agents blocking the RAS such as ACEIs or aliskiren.

DOSAGE AND ADMINISTRATION

Dosage:

General target population:

A patient whose blood pressure is not adequately controlled on monotherapy may be switched to combination therapy with Address. The recommended dose is one tablet per day. 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 may be switched to Address containing the same component doses. Both amlodipine and valsartan monotherapy can be taken with or without food. It is recommended to take Address with some water.

Special Population:

Renal impairment:

No dose adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment:

Due to amlodipine and valsartan, caution should be exercised when administering Address to patients with hepatic impairment or biliary obstructive disorders. Starting with the lowest available dose of amlodipine should be considered.

Pediatric patients (below 18 years):

Address is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy.

Geriatric patients (aged 65 years or above):

Since both components of the combination are equally well tolerated when used at similar doses in elderly (aged 65 years or above) or younger patients, no dose adjustment of the starting dose is required. Starting with the lowest available dose of amlodipine should be considered.

SPECIAL INSTRUCTIONS TO THE PHYSICIAN

Overdosage: There is no experience of overdosage with Address yet. The major symptom of overdosage with valsartan is possibly pronounced hypotension with dizziness. Overdosage with amlodipine may result in excessive peripheral vasodilation and possibly reflux tachycardia. Marked and potentially prolonged systemic hypotension upto and including shock with fetal outcome have been reported. Clinically significant hypotension due to amlodipine overdosage 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.

If the ingestion is recent, induction of vomiting or gastric lavage may be considered.

Administration of activated charcoal to healthy volunteers immediately or up to 2 hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Both valsartan and amlodipine are unlikely to be removed by hemodialysis.

STORAGE

Store in a cool, dry and dark place below 25 ºC. Keep all the medicines out of children's reach.

PRESENTATION

Address 5/80 mg & 5/160 mg are available in 14 film coated tablets, respectively.

*Scotmann Specs. **265th Registration Board Meeting (DRAP)

خوراک: ڈاکٹر کی ہدایت کے مطابق۔

احتیاط: روشنی، نمی اور گرمی سے بچائیں۔

25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر محفوظ کریں۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

مستند ڈاکٹر کے نسخہ پر فروخت اور استعمال کریں۔

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