Valday Tablets

(Amlodipine / Valsartan) Tablet USP

5mg/80mg, 5mg/160mg & 10mg/160mg

COMPOSITION:

Valday Tablets 5mg/80mg
Each film coated tablet contains:
Amlodipine (as Besilate) BP 5mg
Valsartan USP 80mg
Finished Product Specs.: USP

Valday Tablets 5mg/160mg
Each film coated tablet contains:
Amlodipine (as Besilate) BP 5mg
Valsartan USP 160mg
Finished Product Specs.: USP

Valday Tablets 10mg/160mg
Each film coated tablet contains:
Amlodipine (as Besilate) BP 10mg
Valsartan USP 160mg
Finished Product Specs.: USP

DESCRIPTION:
Valday is a fixed combination of Amlodipine and Valsartan for the treatment of Hypertension.

CLINICAL PHARMACOLOGY

Mechanism of Action
Amlodipine and Valsartan are antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension. The combination of these substances has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine
Amlodipine inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and reduction in blood pressure.

Valsartan
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.

Pharmacokinetics

Amlodipine
Absorption
After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6 to12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

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

Metabolism
Amlodipine is extensively (approximately 90%) metabolized in the liver to inactive metabolites.

Excretion
Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7 to 8 days. 10% of the parent compound 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 to 4 hours. Mean absolute bioavailability is 23%. Valsartan can be given with or without food.

Distribution
Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Metabolism
Valsartan is not metabolized to a high extent as only about 20% of dose is recovered as metabolites.
Excretion
Valsartan is primarily eliminated in feces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. The half-life of valsartan is 6 hours.

INDICATIONS
Valday (Amlodipine/Valsartan) is indicated for the treatment of:
- Hypertension.
- Patients whose blood pressure is not adequately controlled on either monotherapy.
- Patients who are likely to need multiple drugs to achieve their blood pressure goals.

DOSAGE AND ADMINISTRATION
The recommended dose of Valday (Amlodipine / Valsartan) is one tablet per day. Valday can be used with or without food and it is recommended to take Valday with some water.

Valday (Amlodipine / Valsartan) Tablets 5mg/80mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 80mg alone.

Valday (Amlodipine / Valsartan) Tablets 5mg/160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 5mg or valsartan 160mg alone.

Valday (Amlodipine / Valsartan) Tablets 10mg/160mg may be administered in patients whose blood pressure is not adequately controlled with amlodipine 10mg or valsartan 160mg alone or with Valday (Amlodipine / Valsartan) Tablets 5mg/160mg.

The dosage can be increased after 1 to 2 weeks of therapy 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.

ADVERSE REACTIONS
Common:
Nasopharyngitis, influenza, hypokalemia, headache, asthenia, fatigue, facial edema, flushing, hot flush, edema, edema peripheral and pitting edema.

Uncommon:
Anorexia, hypercalcemia, hyperlipidemia, hyperuricemia, hyponatremia, coordination abnormal, dizziness, dizziness postural, paraesthesia, somnolence, visual impairment, vertigo, palpitations, tachycardia, orthostatic hypotension, cough, pharyngolaryngeal pain, abdominal discomfort, abdominal pain upper, constipation, diarrhoea, dry mouth, nausea, erythema, rash, arthralgia, back pain and joint swelling.

Rare:
Hypersensitivity, anxiety, visual disturbance, tinnitus, syncope, hypotension, exanthema, hyperhidrosis, pruritus, muscle spasm, sensation of heaviness, pollakiuria, polyuria and erectile dysfunction.

CONTRAINDICATIONS
- Known hypersensitivity to the amlodipine, valsartan or to any of the excipients.
- Pregnancy (As amlodipine/valsartan comes in Pregnancy Category D) & lactation
- Concomitant use of angiotensin receptor antagonists (ARBs) – including valsartan – or of angiotensin-converting enzyme inhibitors (ACEIs) with aliskiren in patients with Type 2 Diabetes.

PRECAUTIONS
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 of combination of amlodipine / valsartan or close medical supervision at the start of treatment is recommended.

Hyperkalemia
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
Combination of amlodipine/valsartan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Hepatic impairment
Amlodipine/valsartan is contraindicated in patients with severe 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 amlodipine/valsartan combination to patients with hepatic impairment or biliary obstructive disorders. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80mg valsartan. Amlodipine dosage recommendations have not been established in patients with mild to moderate hepatic impairment. When recommending amlodipine/valsartan, the lowest available dose of amlodipine component should be used.

Renal impairment
No dosage adjustment of amlodipine/valsartan combination is required for patients with mild to moderate renal impairment. However, no data is available for severe cases (creatinine clearance < 10 mL/min.) and caution is therefore advised. Monitoring of potassium levels and creatinine is advised in moderate renal impairment.

Angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue, has been reported in patients treated with valsartan. Combination of amlodipine /valsartan should be discontinued immediately in patients who develop angioedema and should not be re-administered.

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

Elderly (age 65 years and above)
In elderly patients, caution is required when increasing the dosage. While recommending amlodipine/valsartan, the lowest available dose of amlodipine component should be used.

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

DRUG INTERACTIONS
No drug interaction studies have been conducted with amlodipine/valsartan with other drugs, although studies have been conducted with the individual amlodipine and valsartan components, as described below. Other 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.

Amlodipine
CYP3A4 Inhibitors: A study in elderly patients has shown that diltiazem inhibits the metabolism of amlodipine, probably via CYP3A4 (plasma concentration increased 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). 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. In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin (glyceryl trinitrate), digoxin, warfarin, atorvastatin, aluminum/magnesium antacid, cimetidine, non-steroidal anti-inflammatory drugs, antibiotics, ethanol and oral hypoglycemic drugs.
Cyclosporine: The pharmacokinetics of cyclosporine were not altered when cyclosporine was co-administered with amlodipine in renal transplant patients. The patients were not taking corticosteroids.
Grapefruit juice: Grapefruit juice is known to inhibit the cytochrome P450 system, thereby affecting the pharmacokinetics of drugs such as calcium channel blockers.
Sildenafil: When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect, and has no effect on the pharmacokinetics parameters of amlodipine.

Valsartan
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported 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. Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin etc.) required caution and frequent monitoring of potassium levels. The use of an ACE inhibiting drug (ACE-inhibitors or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-exiting renal impairment. 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. As valsartan is not metabolized to a significant extent, clinically relevant drug-drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are not expected with valsartan. Although valsartan is highly bound to plasma proteins, in vitro studies have not shown any interaction at this level with a range of molecules which are also highly protein bound, such as diclofenac, furosemide, and warfarin.

OVERDOSAGE:
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 the 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 amlodipine/valsartan 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 hemodialysis.

STORAGE CONDITIONS:
- Store below 30°C.
- Protect from heat, light and moisture.

AVAILABILITY:
- **Valday** 5mg/80mg Tablets : Pack of 14 film coated tablets.
- **Valday** 5mg/160mg Tablets : Pack of 14 film coated tablets.
- **Valday** 10mg/160mg Tablets : Pack of 14 film coated tablets.

Keep all medicines out of the reach of children.

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Manufactured by :
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