ANGINET

Valsartan

Description:

ANGINET (Valsartan) is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II (It has a wide variety of physiological effects, including direct and indirect involvement in the regulation of blood pressure. As a potent vasoconstrictor, angiotensin II exerts a direct pressor effect. In addition, it promotes Sodium retention and stimulation of aldosterone secretion).

Administration of **ANGINET** to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

Properties:

In most patients, after administration of a single oral dose of Valsartan, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4 - 6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2 - 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of Valsartan has not been associated with rebound hypertension or other adverse clinical events.

Absorption of Valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability of Valsartan is 23%.

Valsartan is highly bound to serum protein (94 - 97%), mainly serum albumin. Steady-state volume of distribution is low (about 17 L). Plasma clearance is relatively slow (about 2 L/h) when compared with hepatic blood flow (about 30 L/h). Of the absorbed dose of Valsartan, 70% is excreted in the feces and 30% in the urine, mainly as unchanged compound.

Indications:

– Treatment of hypertension.

– Treatment of heart failure (NYHA class II-IV) in patients receiving usual therapy such as diuretics, digitalis and either ACE inhibitors or, beta-blockers but not both; presence of all these standard therapies is not mandatory.

In these patients, **ANGINET** improves morbidity, primarily via reduction in hospitalization period.

Dosage and administration:

ANGINET can be taken either with or without food.

Hypertension: The recommended dose of **ANGINET** is 80 mg once daily, irrespective of race, age or gender. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 160 mg, or a diuretic may be added.

No dosage adjustment is required for patients with renal impairment or hepatic impairment of non-biliary origin and without cholestasis.

ANGINET may also be administered with other antihypertensive agents.

Heart failure: The recommended starting dose of **ANGINET**is 40 mg twice daily. Up titration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

Evaluation of patients with heart failure should always include assessment of renal function.

In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80mg. **ANGINET** is contraindicated in patients with severe hepatic impairment and in patients with cholestasis.

Contraindications:

– Hypersensitivity to any component of this medicine.

– Pregnancy.

– Have recently had a kidney transplant.

– Primary aldosteronism.

– Severe hepatic impairment, biliary cirrhosis and cholestasis.

Precautions:

Sodium- and/or volume-depleted patients: In severely Sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan, for example by reducing the diuretic dose.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an I.V. infusion of normal saline solution. Treatment can be continued once the blood pressure has stabilized.

Renal artery stenosis: Since other drugs that affect the renin-angiotensin-aldosterone system may increase blood urea and serum creatinine in patients with bilateral or unilateral renal artery stenosis, monitoring is recommended as a safety measure upon Valsartan treatment.

Special populations

Elderly: A somewhat higher systemic exposure to Valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Children: The safety and efficacy of Valsartan have not been established in children.

Impaired renal function: Dose adjustment is not required in patients with renal impairment (renal clearance accounts for only 30% of total plasma clearance). In severe cases (creatinine clearance < 10 mL/min.) no data are available, and therefore caution is advised. No studies have been performed in patients undergoing dialysis. However, Valsartan is highly bound to plasma protein and is unlikely to be removed by dialysis.

Hepatic impairment: No dose adjustment for Valsartan is necessary in patients with hepatic impairment of non-biliary origin and without cholestasis (Valsartan does not undergo extensive metabolism). The AUC with Valsartan has been observed to approximately double in patients with biliary cirrhosis or biliary obstruction. Valsartan is mostly eliminated unchanged in the bile. Patients with biliary obstructive disorders showed lower Valsartan clearance; particular caution should be exercised when administering Valsartan to these patients.

Heart failure: Caution should be observed when initiating therapy with Valsartan in patients with heart failure.

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 inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and, rarely, acute renal failure and/or death. Evaluation of patients with heart failure should always include assessment of renal function.

In patients with heart failure, the triple combination therapy (ACE inhibitor, beta-blocker and angiotensin II receptor blocker), Valsartan is not recommended.

Effects on ability to drive and use machines: As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Use during pregnancy and lactation:

Pregnancy category C/D (2nd and 3rd trimesters)

Pregnancy: Due to the mechanism of action of angiotensin II antagonists, a risk for the fetus cannot be excluded. In utero exposure to angiotensin converting enzyme inhibitors given to pregnant women during the 2nd and 3rd trimesters has been reported to cause injury and death to the developing fetus. As for any of drug that also acts directly on the renin-angiotensin-aldosterone system, Valsartan should not be used during pregnancy. If pregnancy is detected during therapy, Valsartan should be discontinued as soon as possible.

Lactation: It is not known whether Valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Thus, it is not advisable to use Valsartan in lactating mothers.

Drug interactions:

- No drug interactions of clinical significance have been found. Drugs which have been studied in clinical trials include: Cimetidine, Warfarin, Furosemide, Digoxin, Atenolol, Indomethacin, Hydrochlorothiazide, Amlodipine and 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.
- Concomitant use of potassium-sparing diuretics (e.g. Spironolactone, Triamterene and Amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine. If co medication is considered necessary, caution is advisable.

Side effects:

Side effects showing an incidence of 1% or more in the Valsartan treatment group (irrespective of their causal association): Headache, dizziness, viral infection, upper respiratory tract infection, coughing, diarrhea, fatigue, rhinitis, sinusitis, back pain, abdominal pain, nausea, pharyngitis, ar-thralgia.

Other side effects with a frequency below 1% included: Oedema, asthenia, insomnia, rash, decreased libido, vertigo. It is unknown whether these effects were causally related to Valsartan therapy or not. Post-marketing data revealed very rare cases of angioedema, rash, pruritus and other hypersensitivity reactions including serum sickness and vasculitis. Low blood pressure with or without symptoms such as dizziness and fainting when standing up.

Decreased kidney function (signs of renal impairment).

Laboratory findings:

No special monitoring of laboratory parameters is necessary for patients with essential hypertension receiving Valsartan therapy.

In rare cases, Valsartan may be associated with decreases in hemoglobin and hematocrit.

Neutropenia was observed in 1.9% of patients treated with Valsartan versus 1.6% of patients treated with an ACE inhibitor.

In controlled clinical trials in hypertensive patients, significant increases in serum creatinine, potassium and total bilirubin were observed, respectively, in 0.8%, 4.4%, and 6% of patients treated with Valsartan versus 1.6%, 6.4% and 12.9% of those treated with an ACE inhibitor.

Occasional elevations of liver function values were reported in patients treated with Valsartan.

Overdosage:

Although there is no experience of overdosage with Valsartan, the major sign that might be expected is marked hypotension. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be I.V. infusion of normal saline solution.

Valsartan is unlikely to be removed by hemodialysis.

Storage conditions:

Store in controlled room not above 30°C.

Presentation:

ANGINET 40: Each film coated tablet contains Valsartan 40 mg in packs of 30 tablets.

ANGINET 80: Each film coated tablet contains Valsartan 80 mg in packs of 30 tablets.

ANGINET 160: Each film coated tablet contains Valsartan 160 mg in packs of 30 tablets.

Hospital packs are also available.

Excipients:

Microcrystalline Cellulose, Colloidal silicon dioxide, Cross Povidone, Magnesium Stearate, Opadry O-YL, Yellow Iron Oxide & Red Iron Oxide.

Marketing Authorization Holder:

MS Pharma Saudi,Riyadh, Kingdome Saudi Arabia.

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Manufacturer by:

United Pharmaceutical Mfg. Co. Ltd. - Jordan for MS Pharma-Saudi.

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To report any side effect(s):

•Saudi Arabia:

-National Pharmacovigilance and Drug SafetyCentre (NPC) :
Fax: +966-11-205-7662
Call NPC at +966-11-2038222
SFDA Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: www.sfda.gov.sa

•Other GCC States:

Please contact the relevant competent authority.

f. Council of Arab Health Ministers

This is a Medicament

• Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
• Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
• The doctor and the pharmacist are experts in medicine, its benefits and risks.
• Do not by yourself interrupt the period of treatment prescribed for you.
• Do not repeat the same prescription without consulting your doctor.
• Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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