Diostar®
valsartan

Pharmacological Properties

Diostar® (valsartan) is an orally active, specific angiotensin (AT)II receptor antagonist.

The active hormone of the renin-angiotensin- aldosterone system (RAAS) is angiotensin II, which is formed by angiotensin- converting enzyme(ACE) from angiotensin I. Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide range of physiological effects, including in particular both direct and indirect involvement in the regulation of blood pressure.

As a potent vasoconstrictor angiotensin II exerts a direct pressor response. It also promotes sodium retention and stimulates aldosterone secretion.

Valsartan is an orally active, specific angiotensin (AT)II receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to further counterbalance the effect of the AT_1 receptor.

Valsartan exhibits no partial agonist activity at the AT_1 receptor. Its affinity for AT_1 receptors is approximately 20,000 times greater than for AT_2 receptors.

Valsartan does not inhibit ACE (= kininase II), the enzyme that converts angiotensin I to angiotensin II receptor and degrades bradykinin. Angiotensin II receptor antagonists are unlikely to cause cough since they have no effect on ACE and do not potentiate bradykinin or substance P. In clinical studies comparing valsartan with an ACE inhibitor, the incidence of dry cough was significantly (p<0.5) lower in patients treated with valsartan than in those treated with the ACE inhibitor (2.6% versus 7.9%). In a clinical trial investigating patients with a history of dry cough during ACE inhibitor therapy, the incidence of cough was 19.5% among patients receiving valsartan and 19.0% among those receiving a thiazide diuretic, as compared to 68.5% among those treated with ACE inhibitor (p<0.05).

Valsartan does not affect other hormone receptors or ion channels known to play an important role in cardiovascular regulation.

Clinical efficacy

In patients with hypertension, valsartan lowers blood pressure without affecting heart rate.

In most patients the onset of antihypertensive effect occurs within 2 hours following a single oral dose, with the maximum effect being achieved after 4-6 hours. Blood pressure reduction is maintained over a period of 24 hours following ingestion. The maximum reduction in blood pressure is generally attained 2-4 weeks after the start of treatment and is maintained during long-term therapy. Concomitant administration with hydrochlorothiazide results in a significant additional reduction in blood pressure.

Withdrawal of valsartan does not bring about rebound hypertension or other adverse effects. Valsartan does not alter fasting levels of total cholesterol, triglycerides, serum glucose or uric acid in hypertensive patients.

Heart failure

Haemodynamics and neurohormones: In a haemodynamic study of 116 patients (36.3% NYHA II,36% NYHA III and 17.7% NYHA IV), all whom were untreated with ACE inhibitors for at least 6 months prior to enrollment, valsartan significantly improved pulmonary capillary wedge pressure, systemic vascular resistance, systolic blood pressure and cardiac output after 28 days of treatment. In the long-term Val-HeFT study, plasma norepinephrine and brain natriuretic peptide (BNP) were significantly reduced from baseline in the valsartan group compared to placebo.

Clinical study

Val HeFT (Valsartan Heart Failure Trial) was a multinational, double-blind study involving 5010patients with NYHA class II (62%) to IV (2%) heart failure and left ventricular ejection fraction (LVEF) <40%. Baseline therapy was chosen by the attending physician, and the patients were randomized to placebo or valsartan, which was titrated form 40mg twice daily to the highest tolerated dose, or 160mg, twice daily. The group receiving no concomitant ACE inhibitor therapy comprised 181 patients on placebo and 185 on valsartan. Patients were kept under observation for an average of about 2 years. There were primary endpoints, both assessed by time to first event: total mortality and heart failure – related morbidity. The latter was defined as total mortality, sudden death with resuscitation, hospitalization for heart failure, or need for intravenous inotropic or vasodilatorly drugs for at least 4 hours.

Valsartan improved heart-failure-related morbidity in the subgroup of patients (7%) who did not receive ACE inhibitor but not in the group receiving concomitant ACE- inhibitor therapy. The following data relate to the subgroup who did not receive an ACE inhibitor.

Patients given valsartan showed an increase in ejection fraction and a reduction in left ventricular internal diastolic diameter (LVIDD), as compared with those given placebo.

Effects were generally consistent across age- and gender – defined subgroups. The number of black patients was too small to permit a meaningful assessment of this subgroup.

	Placebo (n=181)	Valsartan (n=185)	Hazard ratio (95% CI)
Heart- failure -related morbidity	77 (42.5%)	46 (24.9%)	0.51 (0.35-0.73)
Percentage of heart- failure- related morbidity cases			
Total morbidity	49 (27.1%)	33 (17.8%)	0.59 (0.37-0.93)
Sudden death with resuscitation	3 (1.7%)	1(0.5%)	0.47(0.04 - 5.28)
Treatment for manifest heart failure	1(0.6%)	0 (0.0%)	-
Hospitalization due to heart failure	51 (28.2%)	24 (13.0%)	0.43 (0.27-0.71)
Cardiovascular mortality	45 (25.1%)	29 (15.7%)	0.61 (0.40-1.02)
Non- fatal morbidity	40 (22.1%)	24 (13.0%)	0.51 (0.26-0.69)

Pharmacokinetics

Absorption

Absorption of valsartan following oral administration is rapid, although the amount absorbed varies considerably. The mean absolute bioavailability of valsartan is 23% (range 23-47). Its pharmacokinetics are linear in the dose range studied. When given once daily valsartan shows little accumulation. Plasma concentrations were found to be similar in males and females.

When valsartan is given with food, the area under the plasma concentration curve (AUC) is reduced by 48% and C_{max} by 59%, but plasma concentration are similar from 8 hours onwards for ingestion with or without food. The reductions in AUC and C_{max} do not result in clinically significant reduction in therapeutic effect, and Diostar® can therefore be given either with or without food.

Distribution

Valsartan is extensively (94-97%) bound to serum proteins, primarily albumin. Steady state is reached within 1 week. The volume of distribution at steady state is approx. 17 litres. Plasma clearance is relatively slow (about 2 litres/hour) compared with hepatic blood flow (about 30 litres / hour).

Elimination

Valsartan displays multiexponential decay kinetics (phase alpha half-life <1h, terminal half-life approx. 9h) Approx. 70% of absorbed valsartan is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

Pharmacokinetics in special patient

Populations

Elderly patients

A somewhat higher systemic exposure to valsartan was observed in some elderly patients (>65 years) as compared to younger volunteers, but this was not found to be clinically relevant.

Patient with impaired renal function

As may be expected for a compound with renal clearance accounting for only 30% of total plasma clearance, no correlation was found between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with impaired renal function. No studies with dialysis patients have been performed. However, as valsartan is highly bound to plasma proteins it is unlikely to be removed by dialysis.

Patients with impaired hepatic function

About 70% of the absorbed dose is excreted via the bile, mainly as unchanged compound. Valsartan does not undergo extensive biotransformation and, as may be expected, there is no correlation between systemic exposure to valsartan and the degree of liver function impairment. Dose adjustment is therefore not necessary in patients with hepatic failure of non-biliary origin and without cholestasis. The AUC of valsartan was approximately doubled in patients with biliary cirrhosis or biliary obstruction.

In patients with heart failure the time to peak plasma level and elimination half-life of valsartan are similar to those in healthy volunteers.

Over the clinical dose range (40 to 160 mg twice daily), the AUC and C_{max} of valsartan increased in a liner fashion and virtually proportionally to the dose. The mean accumulation factor is approx 1.7.

The apparent clearance of valsartan following oral administration is approx 4.5l/h. Age has no effect on apparent clearance in patients with heart failure.

Indications

- Treatment of mild and moderate essential hypertension.
- Mild to moderate heart failure (NYHA class II and III), normally in combination with diuretics and digitalis, if treatment with ACE inhibitors is unsuitable due to adverse effects specifically attributable to ACE inhibitors (cough). Adverse effects resulting from general influence of ACE inhibitor therapy on the renin-angiotensin- aldosterone system (e.g. progressive renal failure, hyperkalaemia) do not constitute an indication for Diostar®.

Dosage and administration

Diostar® can be taken with liquid during or between meals. It is recommended that Diostar® be taken at the same time every day, e.g. in the mornings for patients with hypertension and evenings and evenings for patients with heart failure.

Essential hypertension

The recommended dose of Diostar® is 80mg once daily, irrespective of race, age or gender.

A substantial antihypertensive effect is attained within two weeks and maximum effect is seen after four weeks. In the event of inadequate reduction of blood pressure the daily dose may be increased to 160mg and up to320 mg or diuretic may be added.

Dose adjustment is not necessary in patients with impaired renal function or hepatic failure of non-biliary origin and without cholestasis.

Diostar® may be co-administered with other antihypertensives.

Heart failure

The recommended starting dose is 40mg valsartan (equivalent to half an 80mg tablet) twice daily. Depending on tolerability, the dose should gradually be increased, first to 80mg valsartan twice daily, then to 160mg valsartan twice daily. If a diuretic is administered concomitantly, a reduction in the dose of the diuretic should be considered. In clinical studies, the maximum daily dose was 320mg valsartan (160mg valsartan twice daily).

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

There is no experience of the therapeutic use of Diostar® in children.

Contraindications

- Hypersensitivity to any of the components of Diostar®.
- Pregnancy.
- There is no experience with Diostar® in patients with severe renal function impairment (creatinine clearance <10ml / min).
- Diostar® is contraindicated in patients with hereditary angioedema or in those with a history of angioedema developing during treatment with ACE inhibitor or angiotensin II receptor antagonist.

Adverse effects

Adverse events which were observed more frequently with valsartan than with placebo in clinical studies and which originate form individual reports are listed according to organ class.

For very rare, rare and uncommon adverse effects that are not detectable in the context of clinical studies, a cumulative search was performed in the safety database.

Very common (>1/10), common (>1/100 to <1/10), uncommon (>1000 to <1/100) rare (>1/10000to <1/1000), very rare (<1/10000).

Blood and lymphatic system disorders

Very rare: Neutropenia

Ear and labyrinth disorders

Uncommon: Vertigo

Gastrointestinal disorders

Uncommon: Diarrhoea, abdominal pain

Very rare: Nausea, vomiting

General disorders

Uncommon: Fatigue

Very rare: Asthenic conditions (including weakness and asthenia), peripheral oedema

Immune system disorders

Very rare: Hypersensitivity reactions such as serum sickness

Infections

Common: Viral infections

Uncommon: Upper respiratory tract infections

Laboratory tests

Common: increase in blood creatinine and urea

Very rare increase in blood bilirubin, reduction in blood haemoglobin / haematocrit, liver laboratory abnormalities.

Metabolism

Common: Increase in potassium

Musculoskeletal and connective tissue disorders

Very rare: Arthralgia, back pain

Nervous system disorders

Very rare: Headache, light-headedness

Pregnancy, puerperium and perinatal conditions

Very rare: Fetal complications

Psychiatric disorders

Very rare: insomnia, reduced libido

Renal and urinary disorders

Rare: Impaired renal function

Respiratory, thoracic and mediastinal disorders

Rare: Cough

Very rare: Rhinitis, sinusitis, pharyngitis

Skin and subcutaneous tissue disorders

Very rare: Angioedema, exanthema, pruritus, cutaneous vasculitis, rash

Vascular disorders

Very rare: Hypotension*

* In clinical studies these adverse effects were observed more frequently in patients with heart failure

Preclinical data

In a variety of preclinical safety studies conducted in several animal species, there was no evidence of systemic or target organ toxicity, apart from feto-toxicity. Offsprings of rats given 600mg /kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay. The main preclinical safety findings are attributed to the pharmacological action of the compound and have not been demonstrated to have any clinical significance.

There was no evidence of mutagenicity, clastogenicity or carcinogenicity.

Laboratory findings

In rare cases valsartan therapy may be associated with a reduction in haemoglobin and haematocrit .In controlled clinical studies, 0.8% and 0.4% of patients receiving Diostar® showed a significant (>20%) reduction in haematocrit and haemoglobin, respectively. In comparison, 0.1% of patients receiving placebo showed a reduction in haematocrit or haemoglobin.

In controlled clinical trials, neutropenia was observed in 1.9% patients treated with valsartan and 1.6% patients treated with an ACE inhibitor.

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

Increases in liver function values were occasionally reported in patients treated with valsartan.

No special monitoring of laboratory parameters is necessary in patients with essential hypertension receiving valsartan therapy.

In heart failure patients, increases of more than 50% in serum creatinine were observed in 3.9% of valsartan – treated patients compared to 0.9% of placebo-treated patients. In these patients increases of more than 20% in serum potassium were observed in 10% of valsartan – treated patients compared to 3.1% of placebo- treated patients.

In heart failure trials, increases of more than 50% in blood urea were observed in 16.6% of patients treated with valsartan as compared to 6.3% of patients treated with placebo.

Warnings and precaution

Sodium depletion and /or volume depletion

In rare cases symptomatic hypotension may occur at the start of Diostar® treatment in patients with severe sodium depletion and /or hypovolaemia (e.g. in patients receiving high dose of diuretics).

Prior to the introduction of Diostar®, sodium and / or volume depletion should be corrected or the dosage of a diuretic already in use reduced.

In the event of hypotension, the patient should be placed in the supine position and given an intravenous infusion of physiological saline if necessary. Diostar® treatment may be resumed once the blood pressure has stabilized.

Renal artery stenosis

Short term (4-day) administration of Diostar® to 12 patients with renovascular hypertension secondary to unilateral renal artery stenosis caused an significant changes in renal haemodynamics, serum creatinine or blood urea nitrogen (BUN). However, Since other drugs that affect the renin- angiotensin-aldosterone system (RAAS) may increase blood urea and serum creatinine in patients with unilateral or bilaical renal artery stenosis, monitoring of such patients is recommended as a precautionary measure.

Impaired renal function

Dose adjustment is not necessary in patients with impaired renal function.

Impaired hepatic function

Dose adjustment is not necessary in patients with hepatic failure.

In patients with mild to mild to moderate hepatic failure the daily dose should not exceed 80mg valsartan.

Valsartan is eliminated mainly as unchanged compound via the bile. Elimination is reduced in patients with biliary obstruction . Particular caution is therefore necessary when administering valsartan in such cases.

Heart failure

In general a reduction in blood pressure may occur in patients with heart failure being treated with Diostar®. Caution is recommended in patients with heart failure, particularly at the start of treatment.

On account of the inhibition of the RAAS, changes in renal function should be anticipated in predisposed patients with severe heart failure whose renal function is dependent on the RAAS, treatment with ACE inhibitors and angiotensin II receptor antagonists has been associated with oliguria and / or progressive azotaemia and, in rare cases, acute renal failure and / or death. Monitoring of patients with heart failure should always include assessment of renal function.

In patients with heart failure, the triple combination of an ACE inhibitor, beta blocker and valsartan (an angiotensin II receptor antagonist) is not recommended. This is because the incidence heart-failure –related morbidity and mortality was found to be higher with concomitant administration of beta blockers and ACE inhibitors than with placebo.

There have been no studies of the efficacy and safety of Diostar® in children.

Effects on abbility to drive and use machines

Like other antihypertensives, Diostar® may impair the reaction, the ability to drive and the ability to operate tools and machines. Caution is recommended.

Drug interactions

No clinically relevant interactions with the following substances have been found: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Since valsartan is not metabolized to significant extent, no clinically relevant drug interactions in the form of metabolic induction or inhibition of the cytochrome P450 system are to be expected.

Although valsartan is extensively bound to plasma proteins, in vitro studies have not shown any interaction at this level with a range of other substances that are extensively bound to plasma proteins (e.g diclofenac, furosemide and warfarin).

There is no experience with concomitant use of valsartan and lithium. Regular monitoring of the serum lithium level therefore is recommended in the event of concomitant administration of lithium and Diostar®.

Concomitant administration of potassium –sparing diuretics (e.g spironolactone, triamterene, 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. Caution is therefore indicated when such co-medication is given

Overdose

There is no experience of Diostar® overdosage, but the major sign would probably be marked hypotension. Vomiting should be induced if ingestion is recent. Otherwise, the usual treatment would be intravenous infusion of physiological saline.

Valsartan is unlikely to be removed by haemodialysis.

Use in pregnancy & lactation

Owing to the mechanism of action of angiotensin II receptor antagonists, the possibility of fetal risk cannot be ruled out. Fetal damage and death have been reported in association with use of drugs that directly affect the RAAS during the second and third trimesters. In humans, fetal renal perfusion, which is dependent on the development of the RAAS, begins during the second trimester. The risks associated with Diostar® treatment therefore increase during the second and third trimesters.

Like other drugs that act directly on the RAAS, Diostar® should not be used during pregnancy. It should be discontinued if pregnancy confirmed during the course of treatment.

All neonates who were exposed to the drug in utero should be carefully checked with regard to adequate urine excretion, hyperkalaemia and blood pressure. If necessary, appropriate medical steps (e.g. rehydration) must be taken to remove the drug from the circulation.

Valsartan was excreted in the milk of lactating rats. There have been no studies in breast-feeding women and Diostar® should therefore not be used during lactation.

In-Active Ingredients:

Microcrystaline cellulose, Croscarmellose sodium, Povidone K 30, Colloidal silicon dioxide, Magnesium stearate, Opadry OY-2, White, PD&C red # 40, Purified water.

Storage conditions:

Store below 25°C.

Presentation

Diostar® 80 mg F/C tablet: Valsartan 80mg/tab.
(Available in 30 tab pack)

Diostar® 160 mg F/C tablet: Valsartan 160mg/tab.
(Available in 30 tab pack)

(This is a medicament - keep medicaments out of reach of children.)

- Medicament is a product which affects your health, and the consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, method for 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.

Rev.date..July,2010 I 246 00