ARBITEN Plus

Valsartan / Hydrochlorothiazide.

Antihypertensive

Combination of an angiotensin II receptor antagonist (type AT_1) with a diuretic.

COMPOSITION. Active substances. Valsartan, hydrochlorothiazide.

Arbiten Plus 80/12.5

Film-coated tablets containing 80 mg valsartan and 12.5 mg hydrochlorothiazide.

Arbiten Plus 160/12.5

Film-coated tablets containing 160 mg valsartan and 12.5 mg hydrochlorothiazide.

Arbiten Plus 160/25

Film-coated tablets containing 160 mg valsartan and 25 mg hydrochlorothiazide.

PROPERTIES/ACTIONS

Valsartan. The active hormone of the rennin-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 and specific angiotensin (AT) II receptor antagonist. It acts selectively on the AT_1 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 AT1 receptors is approximately 20000 times greater than for AT_2 receptors. Valsartan dose not inhibit ACE (=kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin. Angiotensin II 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 ($p<0.05$) lower in patients treated with valsartan than in those treated with the ACE inhibitor (2.6% versus 7.9%). In a clinical trial involving 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 an ACE inhibitor ($p<0.05$). In controlled clinical trials the frequency of cough in patients treated with a combination of valsartan and hydrochlorothiazide was 2.9%. Valsartan does not affect other hormone receptors or ion channels known to play an important role in cardiovascular regulation. 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. Combination with hydrochlorothiazide brings about a significant additional reduction in blood pressure. Withdrawal of valsartan does not bring about rebound hypertension or other adverse effects. Valsartan dose not alter fasting levels of total cholesterol, triglycerides, serum glucose or uric acid in hypertensive patients.

Hydrochlorothiazide. The principal site of action of thiazide diuretics is the early distal tubule. It has been shown that a high-affinity receptor in the renal cortex acts as the primary binding site and site of action of the thiazide diuretics, which inhibit NaCl transport in the early distal tubule. The mode of action of thiazides involves inhibition of Na^+Cl^- symporter. Competition for the Cl^- site may affect electrolyte reabsorption. This results directly in equivalent increases in sodium and chloride excretion, and indirectly in a reduction of plasma volume, with consequent increases in plasma rennin activity, aldosterone secretion and potassium excretion, and a fall in serum potassium. Since the renin-aldosterone axis is angiotensin II dependent, co-administration of an angiotensin II receptor antagonist results in a reduction in the potassium loss associated with thiazides.

PHARMACOKINETICS

Valsartan

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±7). 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 Cmax by 59%, but plasma concentrations are similar from 8 hours onwards for ingestion with or without food. The reduction in AUC and Cmax is not accompanied by a clinically significant reduction in therapeutic effect, and valsartan can therefore be taken 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 liters. Plasma clearance is relatively slow (about 2 litres/hour) compared with hepatic blood flow (about 30 litres/hour).

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

Hydrochlorothiazide

Absorption. Hydrochlorothiazide is rapidly absorbed following oral administration (tmax approx. 2 h).

Distribution and elimination. The distribution and elimination kinetics of hydrochlorothiazide are bi-exponential, with a terminal half-life of 6-15 h.

The increase in mean AUC is linear and proportional to dose in the therapeutic range. The kinetics of hydrochlorothiazide do not change with repeated administration. Accumulation is minimal with once daily administration. The absolute bioavailability of hydrochlorothiazide is 60-80% after oral administration. More than 95% of the absorbed dose is excreted unchanged in the urine. There are reports claiming both increased and decreased hydrochlorothiazide bioavailability after ingestion with as opposed to without food. However, these effects are slight and of little clinical significance.

Valsartan/Hydrochlorothiazide. The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not affected to any significant extent by co-administration with hydrochlorothiazide. This interaction has no impact on the use of valsartan/hydrochlorothiazide combination, which controlled clinical trials have shown to exert a clear antihypertensive effect, greater than that elicited by either drug alone.

Pharmacokinetics in special clinical situations

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. Steady-state concentrations of hydrochlorothiazide are higher and systemic clearance is considerably slower in elderly patients compared with young patients. Close monitoring is therefore necessary in elderly patients receiving treatment with hydrochlorothiazide.

Patients with impaired renal function. Valsartan/Hydrochlorothiazide

No dosage adjustment is necessary for patients with creatinine clearance of 30-70 ml/min.

Valsartan

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 (or severe renal failure see Contraindications). No studies have been performed in patients undergoing dialysis. However, as valsartan is highly bound to plasma proteins it is unlikely to be removed by dialysis.

Hydrochlorothiazide

Renal clearance of hydrochlorothiazide occurs by both passive filtration and active secretion into the renal tubule. As is to be expected for a compound which is cleared almost exclusively via the kidneys, its kinetics are very much affected by renal function (see Contraindications). In patients with impaired renal function, mean peak plasma concentrations and AUC values of hydrochlorothiazide are increased and urinary excretion reduced. Owing to the clear reduction in renal clearance, the mean elimination half-life is almost doubled in patients with kidney failure (creatinine clearance 30-70 ml/min). Hydrochlorothiazide can be cleared by dialysis.

Patients with impaired hepatic function. In a pharmacokinetic study in patients with mild to moderate impairment of hepatic function, the concentration of valsatran was approximately double that observed in healthy volunteers. There are no data on use in patients with severe impairment of hepatic function (see Contraindications). Liver disease dose not noticeably alter the pharmacokinetics of hydrochlorothiazide and dose reduction is therefore not necessary.

INDICATIONS/POTENTIAL USES

Substantiated uses. Treatment of mild and moderate essential hypertension in patients whose blood pressure is not adequately controlled by monotherapy. In such patients treatment should be initiated with Arbiten Plus 80/12.5 mg. If the reduction in blood pressure is not sufficient after 3 to4 weeks, Arbiten Plus 160/12.5 mg may be used, with subsequent increase to Arbiten Plus 160/25 mg.

DOSAGE AND ADMINISTRATION. The recommended dose is one Arbiten Plus 80/12.5 mg daily. In the event of an inadequate response after 3-4 weeks' treatment, it may be necessary to continue treatment with one Arbiten Plus 160/12.5 mg tablets daily. Use of Arbiten Plus 160/25 mg tablets is restricted to those patients in whom adequate reduction of blood pressure is not achieved with Arbiten Plus 160/12.5 mg tablets. The maximum antihypertensive effect is seen within 2 to 4 weeks.

Arbiten Plus dose not have to be taken at mealtimes but should be taken with liquid. They can be taken by patients of any age. Adjustment of the recommended dosage is not necessary for patients with mild to moderate renal failure (creatinine clearance > 30 ml/min) or mild to moderate hepatic failure (see Precautions). There is insufficient experience of the therapeutic use of Valsartan/Hydrochlorothiazide in children.

RESTRICTIONS ON USE

Contraindications.

-Hypersensitivity to valsartan or to sulphonamide derivatives.

-Valsartan/hydrochlorothiazide is contraindicated in patients with hereditary angioedema or in those who had developed angioedema during earlier treatment with an ACE inhibitor or angiotensin II receptor antagonists.

-Pregnancy (see Pregnancy and Lactation).

-Severe hepatic failure, biliary cirrhosis or cholestasis.

-Severe renal dysfunction (creatinine clearance <30 ml/min) or anuria.

-Treatment-resistant hypokalaemia, hyponatraemia or hypercalcaemia and symptomatic hyperuricaemia (history of gout or uric acid calculi).

Precautions

Serum electrolyte changes. Concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or with other drugs that may increase potassium levels (e.g. heparin) requires caution. Serum potassium levels should therefore be monitored at regular intervals. Thiazide diuretics have been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides can cause hypomagnesaemia by increasing renal excretion of

magnesium.

Sodium depletion and/or volume depletion: In rare cases symptomatic hypotension may occur at the start of treatment with valsartan/hydrochlorothiazide in patients with severe sodium and/or volume depletion (e.g. those receiving high doses of diuretic). Sodium and/or volume depletion should be corrected before the start of treatment with valsartan/hydrochlorothiazide. If hypotension occurs, the patients should be placed in the supine position and given physiological saline if necessary. Treatment may be resumed once the blood pressure has stabilized.

Renal artery stenosis: There is no experience with valsartan/hydrochlorothiazide in patients with unilateral or bilateral renal artery stenosis or stenosis of a solitary kidney.

Renal failure: No dosage adjustment is necessary for patients with creatinine clearance ≥ 30 ml/min.

Hepatic failure: No dose adjustment is necessary in patients with mild to moderate hepatic failure without cholestasis. Nonetheless, valsartan/hydrochlorothiazide should be used with caution. The pharmacokinetics of hydrochlorothiazide are not significantly affected by hepatic failure.

Systemic lupus erythematosus: Thiazide diuretics can trigger or exacerbate systemic lupus erythematosus.

Other metabolic disturbances: Thiazide diuretics may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid.

Effects on ability to drive and use machines: As with other antihypertensives, caution is recommended when driving or using machines. There have been no studies of the efficacy and safety of valsartan/hydrochlorothiazide in children.

Pregnancy/Lactation: There is evidence of risk to the humans fetus, but this may be outweighed by the therapeutic benefit for the mother. However, owing to the mechanism of action of angiotensin II antagonists, the possibility of fetal risk cannot be ruled out. Fetal damage and death have been reported in association with the use during the second and third trimesters of drugs that directly affect the RAAS. In humans, fetal renal perfusion, which is dependent on the development of the RAAS, begins during the second trimester. The risks associated with valsartan treatment are therefore higher during the second and third trimesters. Like other drugs that act directly on the RAAS, valsartan/hydrochlorothiazide should not be used during pregnancy. They should be discontinued if pregnancy is confirmed during treatment. All neonates exposed to the drug in utero should be carefully examined for adequate excretion of urine, hyperkalaemia and blood pressure. If necessary, appropriate medical steps (e.g. rehydration) must be taken to remove the drug from the circulation. Intrauterine exposure to thiazide diuretics may cause fetal or neonatal thrombocytopenia and be associated with adverse reactions different to those occurring in adults. It is not known whether valsartan passes into human breast milk. It is excreted in the milk of lactating rats. Hydrochlorothiazide crosses the placental barrier and is excreted in breast milk. There have been no studies in breastfeeding women, and valsartan/hydrochlorothiazide should therefore not be used during lactation.

ADVERSE EFFECTS: Reported adverse effects were as follows:

Central nervous system: Common (>5%): Headache.

Occasional (5-01%): Fatigue, dizziness, depression, anxiety, insomnia.

Upper respiratory tract: Occasional (5-01%): Cough, rhinitis, sinusitis, pharyngitis, upper respiratory tract infections, nosebleeds, bronchitis, and dyspnoea.

Gastrointestinal tract: Occasional (5-01%): Nausea, diarrhea, indigestion, abdominal pain.

Lower urinary tract: Occasional (5-01%): Frequent urination, urinary tract infection.

Musculoskeletal system: Occasional (5-01%): Arm or leg pain, arthritis, myalgia, sprains and strains, muscle cramps, back pain, joint pain.

Other: Occasional (5-01%): Asthenia, chest pain, viral infection, visual disturbances, conjunctivitis, oedema, palpitations, impotence. Since the introduction of the product on the market there have been very rare reports of angioedema, rash, pruritus and other hypersensitivity reactions such as serum sickness and vasculitis. There have also been very rare reports of impaired renal function.

Laboratory findings: A reduction of more than 20% in serum potassium was observed in 2.2% of patients treated with valsartan/hydrochlorothiazide and 3.3% of patients who received placebo. An increase in creatinine was noted in 1.4 % of patients treated with valsartan/hydrochlorothiazide and in 1% of patients given placebo in the controlled clinical trials. The following adverse reactions have been reported in association with valsartan alone but not in association with valsartan/hydrochlorothiazide. In rare cases valsartan therapy may be associated with a reduction in haemoglobin and haematocrit. In controlled clinical trials, 0.8% and 0.4 % of patients showed a significant (>20%) reduction in haematocrit and haemoglobin, respectively. In comparison, 0% of patients receiving placebo showed a reduction in haematocrit or haemoglobin. Neutropenia was observed in 1.9% of patients treated with valsartan and 1.8% of patients treated with an ACE inhibitor. In controlled clinical trials, 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 wiyh valsartan. No special monitoring of laboratory parameters is necessary in patients with essential hypertension receiving valsartan therapy.

Valsartan: Other adverse events reported in clinical trials with valsartan, without reference to a possible casual connection, were as follows:

Occasional (5-01%): Joint pain, gastroenteritis, neuralgia, oedema, asthenia, insomnia, rash, decreased libido, dizziness.

A single case of angioedema has been reported.

Hydrochlorothiazide: The following adverse reactions have been reported in patients receiving monotherapy with a thiazide diuretic (including hydrochlorothiazide), in many cases at a higher dose than that contained in valsartan/hydrochlorothiazide:

Electrolyte and metabolic disorders

(see precautions): Common (>5%): Hypokalaemia. Occasional (5-01%): Hyponatraemia, hypomagnesaemia and hyperuricaemia. Rare (<01%): Hypercalcaemia, hyperglycaemia, glycosuria and deterioration of diabetic metabolic status. Isolated cases: Hypochloraemic alkalosis.

Skin: Occasional (5-01%): Urticaria and other types of rash. Rare (<01%): Photosensetivity Isolated cases: Necrotizing vasculitis, toxic epidermal necrolysis, lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.

Gastrointestinal tract: Occasional (5-01%): Loss of appetite, mild nausea and vomiting. Rare (<01%): Abdominal symptoms, constipation, diarrhea, gastrointestinal symptoms. Isolated cases: Pancreatitis.

Liver: Rare (<01%): Intrahepatic cholestasis or jaundice.

Cardiovascular system: Occasional (5-01%): Orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives. Rare (<01%): Cardiac arrhythmia.

Central nervous system: Rare (<01%): Headache, dizziness or light-headedness, sleep disturbances, depression, paraesthesias.

Sensory organs: Visual disturbances, particularly during the first few weeks of treatment.

Blood: Rare (<01%): Thrombocytopenia, occasionally with purpura. Isolated cases: Leucopenia, agranulocytosis, bone-marrow depression, hemolytic anemia.

Other: Occasional (5-01%): Impotence.

Isolated cases: Hypersensitivity reactions, respiratory symptoms including pneumonitis and pulmonary oedema

INTERACTIONS: The antihypertensive effect of valsartan/hydrochlorothiazide may be increased by concomitant use with other antihypertensive drugs. Concomitant use with potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium, or with other drugs that may increase serum potassium (e.g. heparin) requires caution and monitoring of potassium levels. Reversible increases in serum lithium concentrations and increased lithium toxicity have been reported in connection with concurrent use of lithium with ACE inhibitors and thiazide diuretics. There is no experience with concomitant use of valsartan and lithium. Regular checking of the serum lithium level is therefore recommended in the event of co-administration of lithium and valsartan/hydrochlorothiazide. No clinically relevant interactions were found between valsartan alone and any of the following drugs: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide. The following interactions may occur with valsartan/hydrochlorothiazide as a result of its thiazide diuretic constituent: Concomitant administration of non-steroidal anti-inflammatory agents (e.g. salicylic acid derivatives, indomethacin) may attenuate the diuretic and anti-hypertensive activity of the thiazide component of the valsartan/hydrochlorothiazide. Concurrent hypovolaemia may induce acute renal failure. Potassium and/or magnesium loss may be exaggerated by concomitant use with potassium--depleting diuretics (e.g. furosemide), coticosteroids, ACTH, amphotericin B, carbenoxolone, penicillin G, or salicylic acid derivatives. Thiazide-induced hypokalaemia or hypomagnesaemia may increase the risk of arrhythmia in patients taking cardiac glycosides. Thiazide diuretics increase the effect of curare-type musle relaxants. Adjustment of the dosage of insulin or oral antidiabetic agents may be necessary. Co-administration with thiazide diuretics may increase the frequency of hypersensitivity reactions to allopurinol. The risk of amantadine-induced unwanted effects may increase. Thiazides may also potentiate the hyperglycaemic effect of diazoxide. Thiazides may reduce the renal excretion of cytostatic drugs (e.g. cyclophosphamide, methotrexate) and thus increase their myelosuppressive effects. The bioavailability of thiazide diuretics may be increased by concomitant administration of anti-cholinergic agents (e.g. atropine, biperiden), probably as a result of reduced gastrointestinal motility and slowing of the rate of gastric emptying. There have been isolated reports of haemolytic anaemia in connection with concomitant use of hydroclorothiazide and methyldopa. The absorption of thiazide diuretics is decreased by cholestyramine and colestipol.

Co-administration of thiazide diuretics with vitamin D or calcium salts may enhance the hypercalcaemic effect. Concomitant use with ciclosporin may increase the risk of hyperuricaemia and give rise to symptoms of gout.

OVERDOSAGE: There has been no experience thus far of overdosage with valsartan/hydrochlorothiazide. The main sign of overdosage would probably be marked hypotension. The following signs and symptoms may also occur as a result of hydrochlorothiazide overdosage: nausea, drowsiness, hypovolaemia, and electrolyte disturbances, causing arrhythmias and muscle cramps. Management depends on the time since ingestion and the type and severity of the symptoms with measures to stabilize the circulation taking priority. Vomiting should be induced if ingestion is recent. If the interval since ingestion is longer, an appropriate quantity of activated charcoal should be administered. If there is hypotension, the patient should be placed in the supine position and rapidly given fluid and electrolyte replacement. Valsartan cannot be removed by haemodialysis because of its strong plasma protein binding. Clearance of hydrochlorothiazide can, however, be achieved by this means.

OTHER INFORMATION

Store below 30°C.

- A medicament is a product that 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 dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTRIES
UNION OF ARAB PHARMACISTS

Produced by:
JOSWE® medical
Jordan Sweden Medical and Sterilization Co.
Na'ur - Jordan
الأردنية السويدية للمستلزمات الطبية والتعقيم - ناعور - الأردن
www.joswe.com

P331/8-12-2007/R0