Tabuvan®

Valsartan Tablets

Composition:

Tabuvan 40 mg: Each film coated tablet contains: Valsartan 40 mg.
Tabuvan 80 mg: Each film coated tablet contains: Valsartan 80 mg.
Tabuvan 160 mg: Each film coated tablet contains: Valsartan 160 mg.
Tabuvan 320 mg: Each film coated tablet contains: Valsartan 320 mg.
Excipients: Cellulose microcrystalline, crospovidone, colloidal silicone dioxide, magnesium stearate, HPMC, PEG, titanium dioxide, ferric oxide and brilliant blue lake.

Mechanism of action:

The active hormone of the renin-angiotensin-aldosterone system (RAAS) is angiotensin II, which is formed from angiotensin I through angiotensin-converting enzyme ACE. 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, potent, and specific angiotensin II (Ang 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 Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$).

Properties:

Therapeutic effect: Valsartan lowers raised 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. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse effects.
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±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. Ingestion with food reduces the plasma AUC of valsartan by 48% and C_{max} by 59%. Plasma concentrations are similar from about 8 h onwards for with-food and without-food ingestion. The reductions in AUC and C_{max} do not result in a clinically significant reduction in therapeutic effect, and **Tabuvan** 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 approximately 17 litres. Plasma clearance is relatively slow (about 2 litres/h) when compared with hepatic blood flow (about 30 litres/h).
Elimination: Valsartan displays multiexponential decay kinetics (phase α half-life <1 h, terminal half-life approximately 9 h).
Approximately 70% of absorbed valsartan is excreted in the faeces and 30% in the urine, mainly as unchanged compound.

Indications:

Hypertension: Treatment of essential hypertension.
Recent myocardial infarction: Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left ventricular systolic dysfunction after a recent (12 hours to 10 days) myocardial infarction.
Heart failure: Treatment of symptomatic heart failure when Angiotensin Converting Enzyme (ACE) inhibitors cannot be used, or as add-on therapy to (ACE) inhibitors when beta blockers cannot be used.

Contraindications:

Tabuvan is contraindicated for:
- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy.

Pregnancy and Lactation:

There is evidence of risks to the human fetus, but these may be outweighed by the therapeutic benefit for the mother. 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 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 **Tabuvan** treatment therefore increase during the second and third trimesters. Like other drugs that act directly on the RAAS, **Tabuvan** should not be used during pregnancy. It should be discontinued as soon as possible 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.
Valsartan was excreted in the milk of lactating rats. There have been no studies in breastfeeding women and **Tabuvan** should therefore not be used during lactation.

Effects on ability to drive and use machines:

As with other antihypertensives, caution is recommended when driving or using machines.

antagonist, it cannot be excluded that the use of **Tabuvan** may be associated with impairment of the renal function.
Recent-myocardial infarction: The combination of captopril and valsartan has shown no additional clinical benefit, instead the risk for adverse events increased compared to treatment with the respective therapies.
Therefore, the combination of valsartan with an ACE inhibitor is not recommended. Caution should be observed when initiating therapy in post-myocardial infarction patients. Evaluation of post-myocardial infarction patients should always include assessment of renal function.
Use of **Tabuvan** in post-myocardial infarction patients commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.
Heart Failure: In patients with heart failure, the triple combination of an ACE inhibitor, a beta blocker and **Tabuvan** has not shown any clinical benefit. This combination apparently increases the risk for adverse events and is therefore not recommended. Caution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function.
Use of **Tabuvan** in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed.
Pediatric population:
Impaired renal function: Use in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis has not been studied, therefore valsartan is not recommended in these patients. No dose adjustment is required for pediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored during treatment with valsartan. This applies particularly when valsartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Impaired hepatic function: As in adults, **Tabuvan** is contraindicated in pediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with **Tabuvan** in pediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.

Dosage and Administration:

Hypertension: Initial: 80 mg or 160 mg once daily (in patients who are not volume depleted), majority of effects within 2 weeks, maximal effects in 4-6 weeks, dose may be increased to achieve desired effect, maximum recommended dose: 320 mg/day.
Heart failure: Initial: 40 mg twice daily, titrate dose to 80-160 mg twice daily, as tolerated, maximum daily dose: 320 mg. Note: Do not use with ACE inhibitors and beta blockers.
Dose adjustment is not necessary in elderly patients, patients with impaired renal function (creatinine clearance >10 ml/min) or hepatic failure of non-biliary origin and without cholestasis.
Recent-myocardial infarction: In clinically stable patients, therapy may be initiated as early as 12 hours after a myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg, and 160 mg twice daily over the next few weeks. The starting dose is provided by the 40 mg divisible tablet. The target maximum dose is 160 mg twice daily. In general, it is recommended that patients achieve a dose level of 80 mg twice daily by two weeks after treatment initiation and that the target maximum dose, 160 mg twice daily, be achieved by three months, based on the patient's tolerability. If symptomatic hypotension or renal dysfunction occur, consideration should be given to a dose reduction. Valsartan may be used in patients treated with other post-myocardial infarction therapies, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins, and diuretics. The combination with ACE inhibitors is not recommended. Evaluation of post-myocardial infarction patients should always include assessment of renal function.
Pediatric population:
Pediatric Hypertension:
Children and adolescents 6 to 18 years of age:
The initial dose is 40 mg once daily for children weighing below 35 kg and 80 mg once daily for those weighing 35 kg or more. The dose should be adjusted based on blood pressure response. For maximum doses studied in clinical trials please refer to the table below.
Doses higher than those listed have not been studied and are therefore not recommended.

Weight	Maximum dose studied in clinical trials
≥18 kg to <35 kg	80 mg
≥ 35 kg to <80 kg	160 mg
≥ 80 kg to ≤160 kg	320 mg

Children less than 6 years of age:
Safety and efficacy of **Tabuvan** in children aged 1 to 6 years have not been established.
Use in pediatric patients aged 6 to 18 years with renal impairment:
Valsartan is not recommended in pediatric patients with a creatinine clearance <30 ml/min and pediatric patients undergoing dialysis. No dose adjustment is required for pediatric patients with a creatinine clearance >30 ml/min. Renal function and serum potassium should be closely monitored.
Use in paediatric patients aged 6 to 18 years with hepatic impairment:
As in adults, **Tabuvan** is contraindicated in pediatric patients with severe hepatic impairment, biliary cirrhosis and in patients with cholestasis. There is limited clinical experience with **Tabuvan** in pediatric patients with mild to moderate hepatic impairment. The dose of valsartan should not exceed 80 mg in these patients.
Paediatric heart failure and recent myocardial infarction:
Tabuvan is not recommended for the treatment of heart failure or recent myocardial infarction in children and adolescents below the age of 18 years due to the lack of data on safety and efficacy.
Method of administration: Tabuvan can be taken with liquid during or between meals. It is advisable to take **Tabuvan** at the same time every day, e.g. in the morning.

Overdosage:

Although there is no experience of **Tabuvan** overdosage, 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 hemodialysis.

Interactions with other drugs:

Concomitant use not recommended:

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to 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.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels. If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use: Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs. When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Others: In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: Cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

Paediatric population: In hypertension in children and adolescents, where underlying renal abnormalities are common, caution is recommended with the concomitant use of valsartan and other substances that inhibit the renin angiotensin aldosterone system which may increase serum potassium. Renal function and serum potassium should be closely monitored.

Precautions and Warnings:

Hyperkalaemia: Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Impaired renal function: There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients. No dose adjustment is required for adult patients with a creatinine clearance >10 ml/min.

Hepatic impairment: In patients with mild to moderate hepatic impairment without cholestasis, **Tabuvan** should be used with caution.

Sodium and/or volume depletion: 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 **Tabuvan**. Sodium and/or volume depletion should be corrected before starting treatment with **Tabuvan**, for example by reducing the diuretic dose.

Renal artery stenosis: In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of **Tabuvan** has not been established. Short-term administration of **Tabuvan** to 12 patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine or blood urea nitrogen (BUN). However, other drugs that affect the RAAS may increase BUN and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation: There is currently no experience on the safe use of **Tabuvan** in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism: Patients with primary hyperaldosteronism should not be treated with **Tabuvan** as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy: As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Pregnancy: Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started.

Other conditions with stimulation of the renin-angiotensin system: In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II

Side Effects:

	Hypertension	Post-myocardial infarction and/or heart failure
Blood and lymphatic system disorders	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia	Thrombocytopenia
Immune system disorders	Hypersensitivity including serum sickness	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	Increase of serum potassium	Hyperkalaemia, increase of serum potassium
Nervous system disorders		Dizziness, postural dizziness, syncope, headache.
Ear and labyrinth system disorders	Vertigo	Vertigo
Cardiac disorders		Cardiac failure
Vascular disorders	Vasculitis	Hypotension, orthostatic hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	Cough	Cough
Gastrointestinal disorders	Abdominal pain	Nausea, diarrhoea
Hepatobiliary Disorders	Elevation of liver function values including increase of serum bilirubin.	Elevation of liver function values
Musculoskeletal and connective tissue disorders	Myalgia	Myalgia
Renal and urinary disorders	Renal failure and impairment, elevation of serum creatinine	Renal failure and impairment, acute renal failure, Elevation of serum creatinine, increase in Blood Urea Nitrogen
General disorders and administration site conditions	Fatigue	Asthenia, fatigue
Skin and subcutaneous tissue disorders	Angioedema, rash, pruritus	Angioedema, rash, pruritus

Consult your Pharmacist or Physician if any side effect is observed.

Pharmaceutical Precautions:

Store below 30°C.

Do not use beyond the expiry date or if the product shows any sign of deterioration.

Presentations:

Tabuvan 40 mg : Packs of 30 Film Coated Tablets.
Tabuvan 80 mg : Packs of 30 Film Coated Tablets.
Tabuvan 160 mg: Packs of 30 Film Coated Tablets.
Tabuvan 320 mg: Packs of 30 Film Coated Tablets.
Hospital packs are available.

® is a trademark.

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Strictly follow 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 reach of children.

Council of Arab Health Ministers & Union of Arab Pharmacists.

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