# Co-Tabuvan®

## Valsartan / Hydrochlorothiazide Tablets

**Composition:**
**Co-Tabuvan 80 mg/12.5 mg:** Each film coated tablet contains: Valsartan 80 mg and Hydrochlorothiazide 12.5 mg.
**Co-Tabuvan 160 mg/12.5 mg:** Each film coated tablet contains: Valsartan 160 mg and Hydrochlorothiazide 12.5 mg.
**Co-Tabuvan 160 mg/25 mg:** Each film coated tablet contains: Valsartan 160 mg and Hydrochlorothiazide 25 mg.
**Co-Tabuvan 320 mg/12.5 mg:** Each film coated tablet contains: Valsartan 320 mg and Hydrochlorothiazide 12.5 mg.
**Co-Tabuvan 320 mg/25 mg:** Each film coated tablet contains: Valsartan 320 mg and Hydrochlorothiazide 25 mg.
Excipients: Cellulose microcrystalline, crospovidone, colloidal silicone dioxide, magnesium stearate, HPMC, PEG, titanium dioxide, ferric oxide.

### 1. What Co-Tabuvan is and what it is used for?

**Properties:**
**Pharmacodynamics:**
The active hormone of the RAAS is angiotensin II, which is formed from angiotensin I through (ACE). Angiotensin II binds to specific receptors located in the cell membranes of various tissues. It has a wide variety 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. In addition, it promotes sodium retention and stimulation of aldosterone secretion.
**Pharmacokinetics:**
The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan are not markedly affected by the co-administration of hydrochlorothiazide. This observed interaction has no impact on the combined use of valsartan and hydrochlorothiazide, since controlled clinical trials have shown a clear antihypertensive effect, greater than that obtained with drug given alone, or placebo.

**Indications:**
**Co-Tabuvan** is indicated for the treatment of hypertension.
**Co-Tabuvan** is indicated for the treatment of hypertension in patients whose blood pressure is not adequately controlled by monotherapy. These fixed dose combinations should be used as second-line therapy.

### 2. Before you take Co-Tabuvan

**Contraindications:**
**Co-Tabuvan** is contraindicated for patients with known hypersensitivity to any of its components, or other sulfonamides.
Severe hepatic impairment, biliary cirrhosis and cholestasis. Anuria, severe renal impairment (creatinine clearance <30 mL/min).
Refractory hypokalemia, hyponatraemia, hypercalcemia, pregnancy, and symptomatic hyperuricemia.

**Precautions:**
**Effects on ability to drive and use machines:**
As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.
**Pregnancy and Lactation:**
**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 (ACE) inhibitors (a specific class of drugs acting on the renin-angiotensin-aldosterone system-RAAS) given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing fetus. In addition, in retrospective data, first trimester use of (ACE) inhibitors has been associated with a potential risk of birth defects. Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.
There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan. As for any drug that also acts directly on the RAAS, **Co-Tabuvan** should not be used during pregnancy or in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of childbearing potential about the potential risk of these agents during pregnancy. If pregnancy is detected during therapy, **Co-Tabuvan** 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. Hydrochlorothiazide crosses the placenta and is excreted in human milk. Thus, it is not advisable to use **Co-Tabuvan** in lactating mothers.

**Interactions with other drugs:**
The antihypertensive effect may be increased with concomitant use of other antihypertensive drugs.
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may alter potassium levels (heparin, etc.) should be used with caution and with frequent monitoring of potassium.
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazides.
There is no experience with concomitant use of valsartan and lithium. Therefore, monitoring of serum lithium concentrations is recommended during concurrent use.
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. The following potential drug interactions may occur due to the thiazide component of **Co-Tabuvan**: Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of **Co-Tabuvan**.
Concurrent hypovolemia may induce acute renal failure.
It may prove necessary to readjust the dosage of insulin and of oral antidiabetic agents.

**Warnings:**
**Serum electrolyte changes**
Valsartan
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.
Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide has been associated with hyponatraemia and hypochloraemic alkalosis. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.
**Sodium, and/or volume-depleted patients**
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
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 **Co-Tabuvan**. Sodium and/or volume depletion should be corrected before starting treatment with **Co-Tabuvan**.
**Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system**
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone 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. The use of **Co-Tabuvan** in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of **Co-Tabuvan** as well may be associated with impairment of the renal function. **Co-Tabuvan** should not be used in these patients.
**Primary hyperaldosteronism**
Patients with primary hyperaldosteronism should not be treated with **Co-Tabuvan** as their renin-angiotensin system is not activated.
**Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy**
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
**Kidney transplantation**
There is currently no experience on the safe use of **Co-Tabuvan** in patients who have recently undergone kidney transplantation.
**Renal artery stenosis**
In patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of **Co-Tabuvan** has not been established.
**Renal impairment**
No dosage adjustment is required for patients with renal impairment (dreatinine clearance >30 mL/min).
**Hepatic impairment**
In patients with mild to moderate hepatic impairment without cholestasis, no dosage adjustment is required. However, **Co-Tabuvan** should be used with caution. Liver disease does not significantly alter the pharmacokinetics of hydrochlorothiazide.
**Systemic lupus erythematosus**
Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.
**Other metabolic disturbances**
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid.
**Photosensitivity**
Cases of photosensitivity reactions have been reported with thiazides diuretics. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

### 3. How to take Co-Tabuvan?

necessary 160 mg valsartan and 25 mg hydrochlorothiazide or 320 mg valsartan and 25 mg hydrochlorothiazide may be used.
The maximum antihypertensive effect is seen within 2 to 4 weeks.
No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance >30 mL/min). No dosage adjustment is required in patients with mild to moderate hepatic insufficiency of non-biliary origin and without cholestasis.
The safety and efficacy of **Co-Tabuvan** have not been established in children.

**Overdosage:**
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. If the ingestion is recent, vomiting should be induced. Otherwise, the usual treatment would be i.v. infusion of normal saline solution.
Valsartan cannot be eliminated by means of hemodialysis because of its strong plasma binding behaviour, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

### 4. Possible Side Effects

| | Frequency | Valsartan/ hydrochloro-thiazide | Valsartan | Hydrochlorothia-zide |
|---|---|---|---|---|
| Metabolism and nutrition disorders | Uncommon<br>Not known | Dehydration | <br>Increase of serum potassium | |
| Nervous system disorders | Rare<br>Very rare<br>Uncommon<br>Not known | <br><br>Dizziness<br>Paraesthesia<br>Syncope | | Headache |
| Eye disorders | Uncommon | Vision blurred | | |
| Ear and labyrinth disorders | Uncommon | Tinnitus | Vertigo | |
| Vascular disorders | Uncommon<br>Not known<br>Common | Hypotension | Vasculitis | <br><br>Postural hypotension |
| Respiratory thoracic and mediastinal disorders | Uncommon<br>Not known<br><br>Very rare | Cough<br>Non cardiogenic Pulmonary oedema | | <br><br>Respiratory distress including pneumonitis and pulmonary oedema |
| Gastrointe-stinal disorders | Very rare<br>Uncommon<br><br>Common<br><br>Rare | Diarrhea | <br>Abdominal pain | Pancreatitis<br><br>Loss of appetite, mild nausea and vomiting<br>Constipation, gastrointestinal discomfort |
| Musculos-keletal and connective tissue disorders | Uncommon<br>Very rare | Myalgia<br>Arthralgia | | |
| Renal and urinary disorders | Not known | Impaired renal function | Renal failure | |
| General disorders and admi-nistration site conditions | Uncommon | Fatigue | | |
| Investigati-ons | Not known | Serum uric acid increased, serum bilirubin and serum creatinine increased, hypokalae-mia, hyponatrae-mia, elevation of blood urea nitrogen, neutropenia | | |
| Blood and lymphatic system disorders | Not known<br><br>Rare<br><br>Very rare | | Decrease in haemoglobin, decrease in haematocrite, thrombocyto-penia | <br><br>Thrombocytopeni-a sometimes with purpura<br>Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow depression |
| Immune system disorders | Not known<br><br>Very rare | | Other hypersensitiv-ity/allergic reactions including serum sickness | <br><br>Hypersenstivity reactions |
| Hepatobiliary disorders | Not known<br><br>Rare | | Elevation of liver function values | <br><br>Intrahepatic cholestasis or jaundice |
| Skin and subcutaneo-us tissue disorders | Not known<br><br>Common<br><br>Rare<br>Very Rare | | Angioedema, rash, pruritus | <br><br>Urticaria and other forms of rash<br>Photosensitisation<br>Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus |
| Psychiatric disorders | Rare | | | Depression, sleep disturbances |
| Cardiac disorders | Rare | | | Cardiac arrhythmias |
| Reproductive system and breast disorders | Common | | | Impotence |

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

### 5. How to store Co-Tabuvan?

Store below 30 °C.
Do not use beyond the expiry date or if the product shows any sign of deterioration.

### 6. Further information

**Co-Tabuvan 80 mg/12.5 mg:** Packs of 30 Film Coated Tablets.
**Co-Tabuvan 160 mg/12.5 mg:** Packs of 30 Film Coated Tablets.
**Co-Tabuvan 160 mg/25 mg:** Packs of 30 Film Coated Tablets.
**Co-Tabuvan 320 mg/12.5 mg:** Packs of 30 Film Coated Tablets.
**Co-Tabuvan 320 mg/25 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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## 3. How to take Co-Tabuvan?

**Dosage and Administration:**

The recommended dose of **Co-Tabuvan** is 1 film coated tablet per day. When clinically appropriate either 80 mg valsartan and 12.5 mg hydrochlorothiazide or 160 mg valsartan and 12.5 mg hydrochlorothiazide or 320 mg valsartan and 12.5 mg hydrochlorothiazide may be used. When

Manufactured by:
TABUK PHARMACEUTICAL MANUFACTURING COMPANY,
P.O. Box 3633, TABUK-SAUDI ARABIA.

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