United Pharmaceuticals

CO-ANGINET®

Valsartan-Hydrochlorothiazide

Description:
CO-ANGINET® is a combination tablet of Valsartan and Hydrochlorothiazide: Valsartan is an orally active, potent and specific angiotensin II receptor antagonist while Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic.
Properties:
An oral dose of Valsartan 80 mg will inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. After oral administration of Hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.
Valsartan peak plasma concentration is reached 2 to 4 hours after dosing with absolute bioavailability of about 25% while Hydrochlorothiazide is eliminated by the kidney, with a terminal half-life of 5-15 hours.
Valsartan is highly bound to serum proteins (95%), mainly serum albumin indicating that Valsartan does not distribute into tissues extensively while Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.
Valsartan is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney; at least 61% of the oral dose is eliminated as unchanged drug within 24 hours. The elimination half-life is between 5.8 and 18.9 hours.
Indications:
CO-ANGINET® is indicated for the treatment of mild and moderate essential hypertension in patients whose blood pressure is not adequately controlled by monotherapy.
Dosage and administration:
The recommended dose is one tablet of **CO-ANGINET® 80/12.5** taken daily. In the event of an inadequate response after 3 – 4 weeks' treatment, it may be necessary to continue treatment with one **CO-ANGINET® 160/12.5** tablet taken daily. Use of one **CO-ANGINET®** 160/25 daily is restricted to those patients in whom adequate reduction of blood pressure is not achieved with **CO-ANGINET® 160/12.5** tablets.
Patient notes:
- The maximum antihypertensive effect is seen within 2 – 4 weeks.
- **CO-ANGINET®** should be swallowed with liquid and can be taken independent of mealtimes.
- **CO-ANGINET®** can be taken by patients of any age but there is insufficient experience of the therapeutic use in children and adolescents.
- Dose adjustment is not necessary in patients with mild to moderate renal failure (creatinine clearance ≥ 30 ml/min) or mild to moderate hepatic failure.

Contraindications:
- Hypersensitivity to any component of the drug or to sulphonamide derivatives.
- In patients with hereditary angioedema or in those who had developed angioedema during treatment with an ACE inhibitor or angiotensin II receptor antagonist.
- Pregnancy.
- 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 **CO-ANGINET®** treatment in patients with severe Sodium and/or volume depletion (e.g. those receiving high doses of diuretics).
Sodium and/or volume depletion should be corrected before the start of **CO-ANGINET®** treatment.
If hypotension occurs, the patient 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 **CO-ANGINET®** in patients with unilateral or bilateral renal artery stenosis or stenosis of a solitary kidney.
Renal impairment:
No dose adjustment is necessary in patients with creatinine clearance ≥ 30 ml/min.
Hepatic insufficiency:
No dose adjustment is necessary in patients with mild to moderate hepatic failure without cholestasis. Nonetheless, **CO-ANGINET®** 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.
There have been no studies of the efficacy and safety of **CO-ANGINET®** in children and adolescents.
Effects on ability to drive and use machines:
Like other antihypertensives, **CO-ANGINET®** may impair the reactions, the ability to drive and the ability to operate tools and machines. Caution is recommended.
Use during pregnancy and lactation:
Pregnancy category **D**
Pregnancy:
CO-ANGINET® must not be used during pregnancy.
Fetal damage and death have been reported in association with the use during the second and third trimesters of drugs that directly affect the renin-angiotensin-aldosterone system (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, **CO-ANGINET®** should not be used during pregnancy. It should be discontinued if pregnancy is confirmed during treatment. Adequate urine excretion, hyperkalaemia and blood pressure should be carefully examined in all neonates exposed to the drug in utero. 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 side effects different from those occurring in adults.
Lactation:
It is not known whether Valsartan passes into human breast milk. It is excreted in the milk of lactating rates.
Hydrochlorothiazide crosses the placental barrier and is excreted in breast milk. There have been no studies in breastfeeding woman and **CO-ANGINET®** should therefore not be used during lactation.
Drug interactions:
The antihypertensive effect of **CO-ANGINET®** may be increased by concomitant use with other antihypertensive drugs.
Concomitant 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 **CO-ANGINET®**.
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 **CO-ANGINET®** as a result of its thiazide diuretic constituent:
- Concomitant administration of non-steroidal anti-inflammatory drugs (e.g. Salicylic acid derivatives, Indomethacin) may attenuate the diuretic and antihypertensive activity of the thiazide component of **CO-ANGINET®**.
-Acute renal failure may be induced in patients with concurrent hypovolaemia.
- Potassium and/or Magnesium loss may be exacerbated by concomitant use with Potassium-depleting diuretics (e.g. Furosemide), glucocorticoids, ACTH, Amphotericin B, Carbenoxolone, Penicillin G, or Salicylates.
- Thiazide-induced hypokalaemia or hypomagnesaemia may increase the risk of arrhythmia in patients taking cardiac glycosides.
- Thiazide diuretics increase the effect of curare-type muscle 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 hyperglycemic effect of Diazoxide.
- Thiazides may reduce 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 anticholinergic agents (e.g. Atropine, Biperiden), probably as a result of reduced gastrointestinal motility and delayed gastric emptying.
- There have been isolated reports of hemolytic anemia in connection with concomitant use of hydrochlorothiazide 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.

Side effects:
Infections:
Uncommon: viral infection.
Nervous system disorders:
Common: headache, fatigue.
Uncommon: Asthenia, dizziness, insomnia, anxiety.
Rare: Depression.
Eye disorders:
Uncommon: Visual disturbances.
Rare: Conjunctivitis.
Heart:
Uncommon: Palpitations.
Vascular disorders:
Uncommon: Edema.
Respiratory tract:
Common: Cough, rhinitis, sinusitis, Pharyngitis, upper respiratory tract infection.
Uncommon: Bronchitis, dyspnea.
Very rare: Epistaxis.
Gastrointestinal disorders:
Common: Nausea, diarrhea.
Uncommon: Abdominal pain, indigestion.
Musculoskeletal system:
Common: Arm or leg pain, back pain, chest pain.
Uncommon: Joint pain, arthritis, sprains and strains, muscle cramps.
Rare: Myalgia.
Renal and urinary disorders:
Uncommon: frequent urination, urinary tract infection.
Reproductive system and breast disorders:
Common: Impotence.
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:
- Reduction in serum Potassium.
- An increase in creatinine level.

Overdosage:
There has been no experience thus far of overdosage with **CO-ANGINET®**. 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, associated with 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 ingested 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 hemodialysis because of its strong plasma protein binding. Clearance of hydrochlorothiazide, however, can be achieved by this means.
Storage conditions:
Store up to 30°C.
Presentation:
CO-ANGINET® 80/12.5: Each film coated tablet contains Valsartan 80 mg and Hydrochlorothiazide 12.5 mg in packs of 30 tablets.
CO-ANGINET® 160/12.5: Each film coated tablet contains Valsartan 160 mg and Hydrochlorothiazide 12.5 mg in packs of 30 tablets.
CO-ANGINET® 160/25: Each film coated tablet contains Valsartan 160 mg and Hydrochlorothiazide 25 mg in packs of 30 tablets.
Hospital packs are also available.

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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