Summary of Product Characteristics

1. Name of the Medicinal Product:

Co-Anginet® 80/12.5mg film coated Tablets

2. Qualitative and Quantitative Composition:

Each tablet contains 80 mg of Valsartan and 12.5 mg of hydrochlorothiazide as the active ingredients.

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Dosage Form**:** Film coated Tablets
Tablet Description: Pink caplet biconvex film coated tablets, embossed with T 14 on one side & plain on the other side.

4. Clinical Particulars:

4.1 Therapeutic Indications:

Treatment of essential hypertension in adults.

Valsartan/hydrochlorothiazide fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration:

The route of administration: Orally.

Posology:

The recommended dose of Valsartan/hydrochlorothiazide 160 mg/12.5 mg is one film coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.

The clinical response to Valsartan/hydrochlorothiazide should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of valsartan/hydrochlorothiazide 320 mg/25 mg.

The antihypertensive effect is substantially present within 2 weeks.

In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.
Method of administration:

Valsartan/Hydrochlorothiazide can be taken with or without food and should be administered orally with water.

Special populations:

Renal impairment

No dose adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥ 30 ml/min). Due to the hydrochlorothiazide component, **Co-Anginet®**is contraindicated in patients with severe renal impairment (GFR < 30 mL/min) and anuria. Concomitant use of valsartan with aliskiren is contraindicated in patients with renal impairment (GFR < 60 mL/min/1.73 m^2).

Diabetes Mellitus

Concomitant use of valsartan with aliskiren is contraindicated in patients with diabetes mellitus

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg. Valsartan/Hydrochlorothiazide is contraindicated in patients with severe hepatic impairment.

Elderly

No dose adjustment is required in elderly patients.

Paediatric population

Valsartan/hydrochlorothiazide is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications:

- Hypersensitivity to Valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
- Second and third trimester of pregnancy.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance <30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Concomitant use of angiotensin receptor antagonists (ARBs) – including valsartan – or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73m^2).

4.4 Special warnings and precautions for use:
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 Valsartan/Hydrochlorothiazide. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide.

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 Valsartan/ Hydrochlorothiazide 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 Valsartan/Hydrochlorothiazide as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide should not be used in these patients.

Renal artery stenosis:
Valsartan/Hydrochlorothiazide should not be used to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism:
Patients with primary hyperaldosteronism should not be treated with Valsartan/ Hydrochlorothiazide 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).

Renal impairment:
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 ml/min. Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan/Hydrochlorothiazide is used in patients with renal impairment.

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

Hepatic impairment:
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/ Hydrochlorothiazide should be used with caution.

History of angioedema
Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. **Co-Anginet®** should be immediately discontinued in patients who develop angioedema, and **Co-Anginet®** should not be re-administered.

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. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.
Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

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.

General:
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAAS)
Hypotension, syncope, stroke, hyperkalaemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system by combining aliskiren with an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor blocker (ARB) is therefore not recommended.
The use of aliskiren in combination with **Co-Anginet®** is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

4.5 Interaction with other medicinal products and other forms of interaction:

Interactions related to both Valsartan and hydrochlorothiazide:

Concomitant use not recommended:

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. 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.

Concomitant use requiring caution:

Other antihypertensive agents
Valsartan/Hydrochlorothiazide may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta blockers, calcium channel blockers).

***Pressor amines* (e.g. noradrenaline, adrenaline)**
Possible decreased response to pressor amines but not sufficient to preclude their use.

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
NSAIDS can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan/Hydrochlorothiazide and NSAIDs may lead to 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.

Interactions related to valsartan:
Concomitant use not 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.

No interaction
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. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan/ Hydrochlorothiazide.
Interactions related to hydrochlorothiazide:

Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives)
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium.

Medicinal products that could induce torsades de pointes
- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine i.v.)

Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

Digitalis glycosides
Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects favouring the onset of digitalis-induced cardiac arrhythmias.

Calcium salts and vitamin D
Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium.

Antidiabetic agents (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.
Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta blockers and diazoxide
Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)
Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents, apparently due to a decrease in gastrointestinal motility and the stomach emptying rate.

Amantadine
Thiazides, including hydrochlorothiazide, may increase the risk of adverse effects caused by amantadine.

Cholestyramine and cholestipol resins
Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired in the presence of anionic exchange resins.

Cytotoxic agents (e.g. cyclophosamide, methotrexate)
Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

Non- depolarising skeletal muscle relaxants (e.g. tubocurarine)
Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

Ciclosporin
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Alcohol, anaesthetics and sedatives
Potentiation of orthostatic hypotension may occur.

Methyldopa
There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

Carbamazepine

Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatremia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Iodine contrast media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

4.6 Pregnancy and Lactation:
Pregnancy:
Valsartan
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimester of pregnancy.
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.
AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).
Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women expect in rare situations where no other treatment could be used.
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Women of childbearing potential/Contraception in males and females:
Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

Breastfeeding:
No information is available regarding the use of valsartan during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore the use of Valsartan/ Hydrochlorothiazide during breast feeding is not recommended. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

4.7 Effects on Ability to Drive and Use Machines:
Co-Anginet 80/12.5mg F.C. Tablets has no studies on the effect of Valsartan/ Hydrochlorothiazide, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects:
Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

Frequency of adverse reactions with valsartan/hydrochlorothiazide:

Nervous system disorders:
Very rare: Dizziness
Uncommon: Paraesthesia
Not known: Syncope.

Eye disorders:
Uncommon: Vision blurred

Ear and labyrinth disorders:
Uncommon: Tinnitus

Vascular disorders:
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Cough.
Not known: Non cardiogenic pulmonary oedema

Gastrointestinal disorders:
Very rare: Diarrhea

Musculoskeletal and connective tissue disorders:
Uncommon: Myalgia.
Very rare: Arthralgia.

Renal and urinary disorders:
Not known: Impaired renal function

General disorders:
Uncommon: Fatigue.

Investigations:
Not known: Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia.
Frequency of adverse reactions with valsartan:

Blood and lymphatic system disorders:
Not known: Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia.

Immune system disorders:
Not known: Other hypersensitivity/allergic reactions including serum sickness.

Metabolism and nutrition disorders:
Not known: Increase of serum potassium, hyponatraemia.

Very common: Hypokalaemia, blood lipids increased (mainly at higher doses)
Common: Hyponatraemia, hypomagnesaemia, hyperuricaemia
Rare: Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state
Very rare: Hypochloraemic alkalosis

Metabolism and nutrition disorders:
Not known: Increase of serum potassium, hyponatraemia.

Ear and labyrinth disorders:
Uncommon: Vertigo

Vascular disorders:
Not known: Vasculitis.

Gastrointestinal disorders:
Uncommon: Abdominal pain.

Hepatobiliary disorders:
Not known: Elevation of liver function values.

Skin and subcutaneous tissue disorders:
Not known: Angioedema, rash, pruritus.

Renal and urinary disorders:
Not known: Renal failure.

Frequency of adverse reactions with hydrocholothiazide:
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan/Hydrochlorothiazide. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

Blood and lymphatic system disorders:
Rare**:** Thrombocytopenia sometimes with purpura.
Very rare: Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow depression.

Immune system disorders:
Very rare: Hypersenstivity reactions.

Psychiatric disorders:
Rare**:** Depression, sleep disturbances.

Nervous system disorders:
Rare**:** Headache.

Eye disorders
Rare: Visual impairment

Cardiac disorders:
Rare**:** Cardiac arrhythmias.

Vascular disorders:
Common**:** Postural hypotension.

Respiratory, thoracic and mediastinal disorders:
***Very rare*:** Respiratory distress including pneumonitis and pulmonary oedema.

Gastrointestinal disorders:
Common**:** Loss of appetite, mild nausea and vomiting.
Rare: Constipation, gastrointestinal discomfort.
Very rare: Pancreatitis.

Hepatobiliary disorders:
Rare**:** Intrahepatic cholestasis or jaundice.

Renal and urinary disorders
Not known: Renal dysfunction, acute renal failure.

Skin and subcutaneous tissue disorders:
Common**:** Urticaria and other forms of rash.
Rare: Photosensitisation.
Very rare: Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
Not known: Erythema multiform

General disorders and administration site conditions
Not known: Pyrexia, asthenia

Musculoskeletal and connective tissue disorders
Not known: Muscle spasm

Reproductive system and breast disorders:
Common: Impotence.

4.9 Overdose:
Symptoms:
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment:
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.
If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5. Pharmacological Properties:
5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, valsartan and diuretics; ATC code: C09D A03.

Valsartan/hydrochlorothiazide:
In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg & on valsartan 80 mg.
Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide.
Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown.

Valsartan:
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1receptor subtype, which is responsible for the known actions of angiotensin II.
Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.
Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin.

Hydrochlorothiazide:
The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. The primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na^+Cl^- symporter perhaps by competing for the Cl^- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with hydrochlorothiazide.

5.2 Pharmacokinetic Properties:

Valsartan/hydrochlorothiazide:
The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan is 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 anti-hypertensive effect, greater than that obtained with either active substance given alone, or placebo.

Valsartan:
Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation
Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½ß}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug.

Hydrochlorothiazide:
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 h). Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

Distribution
The distribution and elimination kinetics have generally been described by a bi-exponential decay function. The apparent volume of distribution is 4–8 l/kg.
Circulating hydrochlorothiazide is bound to serum proteins (40–70%), mainly serum albumin.

Elimination
For hydrochlorotiazide, >95% of the absorbed dose being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule. The terminal half-life is 6-15 h.

Special populations:
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects.
Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Renal impairment
At the recommended dose of Valsartan/Hydrochlorothiazide no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min.
In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan/Hydrochlorothiazide. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.
Renal clearance of hydrochlorothiazide is composed of passive filtration and active secretion into the renal tubule. As expected for a compound which is cleared almost exclusively via the kidneys, renal function has a marked effect on the kinetics of hydrochlorothiazide.

Hepatic impairment
In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately 2-fold compared with healthy volunteers.

There is no data available on the use of valsartan in patients with severe hepatic dysfunction. Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical Safety Data:
Co-Anginet® is a generic product; accordingly, no need for the preclinical safety data.

6. Pharmaceutical Particulars:
6.1 List of Excipients:

Avicel PH 101

Cross Povidone

Aerosil 200

Magnesium Stearate

Opadry OYL white 28900

Yellow iron oxide

Red iron oxide

6.2 Incompatibilities:
Not applicable

6.3 Shelf Life:
36 months

6.4 Special Precaution for Storage:
Store in controlled room not above 30°C.

6.5 Nature and Content of the Container:
Aluminum /Aluminum Foil
Outer box
Multi folded leaflet

Pack Size:
30 F.C. tablets" 10tablets/blister, 3 blisters/pack".
1000 F.C. tablets" 10tablets/blister, 100 blisters/pack".
Not all pack sizes may be marketed.

6.6 Special precautions for disposal:

Any unused product or waste should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder:
The United Pharmaceutical Mfg. Co Limited.
P.O. Box 69, Amman 11591-Jordan
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8. Marketing Authorization number:
TAN 21 HM 0405

9. Date of first Authorization /renewal of the authorization:
2021-10-09

10. Date of Revision of the Text: