

NEW ZEALAND DATA SHEET

CO-DIOVAN[®]

Valsartan and Hydrochlorothiazide

Film-coated tablets

80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg

Description and composition

Active substances

(S)-N-valeryl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]-valine (INN = valsartan) and 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (= hydrochlorothiazide).

One tablet contains 80 mg valsartan and 12.5 mg hydrochlorothiazide, or 160 mg valsartan and 12.5 mg hydrochlorothiazide, or 160 mg valsartan and 25 mg hydrochlorothiazide, or 320 mg valsartan and 12.5 mg hydrochlorothiazide, or 320 mg valsartan and 25 mg hydrochlorothiazide

List of excipients

Co-Diovan 80/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171); red iron oxide (E172); yellow iron oxide (E172).

Co-Diovan 160/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171); red iron oxide (E172).

Co-Diovan 160/25 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171), red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172).

Co-Diovan 320/12.5 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; black iron oxide (E172), titanium dioxide (E171); red iron oxide (E172);.

Co-Diovan 320/25 mg: Colloidal silicon dioxide; crospovidone; hydroxypropyl-methylcellulose; magnesium stearate; microcrystalline cellulose; polyethylene glycol; talc; titanium dioxide (E171); yellow iron oxide (E172).

Presentations

Film-coated tablets 80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg

Co-Diovan[®] 80/12.5 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 10.2 mm. by 5.4 mm and 3.7 mm in thickness, and weighing approximately 156 mg. The tablets are coloured light orange and imprinted with HGH on one side and CG on the other side.

Co-Diovan 160/12.5 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 15.2 mm by 6.2 mm and 4.4 mm in thickness, and weighing approximately 312 mg. The tablets are coloured dark red and imprinted with HHH on one side and CG on the other side.

Co-Diovan 160/25 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 14.2 mm by 5.7 mm and 4.5 mm in thickness, and weighing approximately 310 mg. The tablets are coloured brown-orange and imprinted with HXH on one side and NVR on the other side.

Co-Diovan 320/12.5 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 17.7 mm by 8.2 mm and 5.6 mm in thickness, and weighing approximately 608 mg. The tablets are coloured pink and imprinted with HIL on one side and NVR on the other side.

Co-Diovan 320/25 mg: Ovaloid, non-divisible, film-coated tablets measuring approximately 17.7 mm by 8.2 mm and 5.6 mm in thickness, and weighing approximately 620 mg. The tablets are coloured yellow and imprinted with CTI on one side and NVR on the other side.

Indications

Treatment of hypertension.

Co-Diovan 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.

Dosage and administration

The recommended dose of Co-Diovan is 1 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 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.

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥ 30 mL/min). Due to the hydrochlorothiazide component, Co-Diovan is contraindicated in patients with anuria (*see Contraindications*) and should be used with caution in patients with severe renal impairment (GFR < 30 mL/min) (*see Warnings and precautions and Further information - Pharmacokinetics*). Thiazide diuretics are ineffective as monotherapy in severe renal impairment (GFR < 30 mL/min) but may be useful in these patients, when used with due caution in combination with a loop diuretic even in patients with GFR < 30 mL/min.

Hepatic impairment

No dosage adjustment is required in patients with mild to moderate hepatic impairment. Due to the hydrochlorothiazide component, Co-Diovan should be used with particular caution in patients with severe hepatic impairment. Due to the valsartan component, Co-Diovan should be used with particular caution in patients with biliary obstructive disorders (*see Contraindications and Warnings and precautions*).

Paediatrics (below 18 years)

The safety and efficacy of Co-Diovan have not been established in children below the age of 18 years.

Contraindications

Known hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients of Co-Diovan.

Pregnancy (see *Warnings and precautions – use in pregnancy and lactation*).

Biliary cirrhosis and cholestasis.

Anuria.

Warnings and precautions

Serum electrolyte changes

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other drugs that may increase potassium levels (heparin, etc.) should be used with caution. Thiazide diuretics can precipitate new onset hypokalemia or exacerbate pre-existing hypokalemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalemia is accompanied by clinical signs (e.g. muscular weakness, paresis, or ECG alterations), Co-Diovan should be discontinued. Correction of hypokalemia and any coexisting hypomagnesemia is recommended prior to the initiation of thiazides. Potassium and magnesium serum concentrations should be checked periodically. All patients receiving thiazide diuretics should be monitored for imbalances in electrolytes, particularly potassium.

Thiazide diuretics can precipitate new onset hyponatremia and hypochloremic alkalosis or exacerbate pre-existing hyponatremia. Hyponatremia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in isolated cases. Regular monitoring of serum sodium concentrations is recommended.

Patients with 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 Co-Diovan. Co-Diovan should be used only after correction of any pre-existing sodium and/or volume depletion otherwise the treatment should start under close medical supervision.

If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an i.v. infusion of normal saline. Treatment can be continued once the blood pressure has stabilized.

Patients with renal artery stenosis

Co-Diovan should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney, since blood urea and serum creatinine may increase in such patients.

Patients with renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment (GFR \geq 30 mL/min). Due to the hydrochlorothiazide component use Co-Diovan with caution in severe renal impairment (GFR <30 mL/min). Thiazide diuretics may precipitate azotemia in patients with chronic kidney disease. They are ineffective as monotherapy in severe renal impairment (GFR <30 mL/min) but may be useful, when used with due caution in combination with loop diuretics even in patients with GFR <30 mL/min (see *Dosage and administration and Further information - Pharmacokinetics*).

Patients with hepatic impairment

In patients with mild to moderate hepatic impairment no dosage adjustment is required. Co-Diovan should be used with particular caution in patients with biliary obstructive disorders and in patients with

severe hepatic impairment (see *Dosage and administration, Contraindications and Further information - Pharmacokinetics*).

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-Diovan should be immediately discontinued in patients who develop angioedema, and Co-Diovan 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 and triglycerides.

Like other diuretics, hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia and precipitate gout in susceptible patients.

Thiazides decrease urinary calcium excretion and may cause mild elevation of serum calcium in the absence of known disorders of calcium metabolism. Since hydrochlorothiazide can increase serum calcium concentrations, it should be used with caution in patients with hypercalcemia. Marked hypercalcemia unresponsive to thiazide withdrawal or ≥ 12 mg/dL may be evidence of an underlying thiazide independent hypercalcemic process.

Pathological changes in the parathyroid gland of patients with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. If hypercalcemia occurs, further diagnostic clarification is necessary.

General

Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Acute Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to week of a drug initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Patients with heart failure/post-myocardial infarction

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 or angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia, and in rare cases with acute renal failure and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of child-bearing potential

As for any drug that also acts directly on the RAAS, Co-Diovan should not be used in women planning to become pregnant. Healthcare professionals prescribing any agents acting on the RAAS should counsel women of child-bearing potential about the potential risk of these agents during pregnancy.

Use in Pregnancy

As for any drug that also acts directly on the RAAS, Co-Diovan should not be used during pregnancy (*see Contraindications*). Due to the mechanism of action of angiotensin II antagonists, a risk for the foetus 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 foetus. In addition, in retrospective data, first trimester use of ACE inhibitors has been associated with a potential risk of birth defects. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction, when pregnant women have inadvertently taken valsartan.

Intrauterine exposure to thiazide diuretics, including hydrochlorothiazide, is associated with fetal or neonatal jaundice or thrombocytopenia, and may be associated with other adverse reactions that have occurred in adults.

If pregnancy is detected during therapy, Co-Diovan should be discontinued as soon as possible (*see Non-clinical safety data*).

Use in 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-Diovan in lactating breast-feeding mothers.

Fertility

There is no information on the effects of valsartan or hydrochlorothiazide on human fertility. Studies in rats did not show any effects of valsartan or hydrochlorothiazide on fertility (*see Non-clinical safety data*).

Effects on ability to drive and use machines

As with other antihypertensive agents, it is advisable to exercise caution when driving or operating machinery.

Non-clinical safety data

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan:hydrochlorothiazide in humans. High doses of valsartan:hydrochlorothiazide (100:31.25 to 600:187.5 mg/kg body weight) caused, in rats, a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (moderate to severe raised plasma urea, increases in plasma potassium and magnesium and mild increases in urinary volume and electrolytes, minimal to slight tubular basophilia, and afferent arteriolar hypertrophy at the highest dose level). In marmosets (30:9.375 to 400:125 mg/kg), the changes were fairly similar though more severe, particularly at the higher dose levels and in the kidney, where the changes developed to a nephropathy, which included raised urea and creatinine. Marmosets also has gastrointestinal mucosal changes at 30:9.373 to 400:125 mg/kg,

Hypertrophy of the renal juxtaglomerular cells was also seen in rats and marmosets. All changes were considered to be caused by the pharmacological action of valsartan:hydrochlorothiazide which is synergistic (potentiation is about tenfold compared to valsartan alone) rather than additive, producing prolonged hypotension particularly in marmosets. For therapeutic doses of valsartan:hydrochlorothiazide in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance. The main preclinical safety findings are attributed to the pharmacological action of the compounds which appear to act synergistically with no evidence of any interaction between the two compounds. In the clinic, the actions of the two compounds are additive, and the preclinical findings have not been demonstrated to have any clinical significance. The combination valsartan:hydrochlorothiazide was not tested for mutagenicity, clastogenicity, or carcinogenicity as there was no evidence for any interaction between the two compounds.

Valsartan

Valsartan has been tested for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

In a variety of preclinical safety studies conducted in several animal species, there were no findings that would exclude the use of therapeutic doses of valsartan in humans. In preclinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, hemoglobin, hematocrit) and evidence of changes in renal hemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient). In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine. Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance. In embryofetal development studies (Segment II) in mice, rats and rabbits, fetotoxicity was observed in association with maternal toxicity in rats at valsartan doses of ≥ 200 mg/kg/day and in rabbits at doses of ≥ 10 mg/kg/day. In a peri- and postnatal development toxicity (segment III) study, the offspring of rats given 600 mg/kg during the last trimester and during lactation showed a slightly reduced survival rate and a slight developmental delay.

Hydrochlorothiazide

Hydrochlorothiazide has been tested for mutagenicity, clastogenicity, reproductive performance and carcinogenicity with negative results.

Adverse effects

Adverse drug reactions reported in clinical trials and laboratory findings occurring more frequently with valsartan plus hydrochlorothiazide versus placebo and individual post-marketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

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.

Table 1 Frequency of adverse drug reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders	
Uncommon	Dehydration
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 edema
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 and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known	Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalemia, Hyponatremia, Elevation of Blood Urea Nitrogen, Neutropenia

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Abdominal pain, abdominal pain upper, anxiety, arthritis, asthenia, back pain, bronchitis, bronchitis acute, chest pain, dizziness postural, dyspepsia, dyspnea, dry mouth, epistaxis, erectile dysfunction, gastroenteritis, headache, hyperhidrosis, hypoesthesia, influenza, insomnia, ligament sprain, muscle spasms, muscle strain, nasal congestion, nasopharyngitis, nausea, neck pain, edema, edema peripheral, otitis media, pain in extremity, palpitations, pharyngolaryngeal pain, pollakiuria, pyrexia, sinusitis, sinus congestion, somnolence, tachycardia, upper respiratory tract infections, urinary tract infections, vertigo, viral infections, vision disturbance

Additional information on the individual components

Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Co-Diovan as well, even if not observed in clinical trials or during post-marketing period.

Table 2 Frequency of adverse drug reactions with valsartan

Blood and lymphatic system disorders	
Not known	Decrease in hemoglobin, decrease in hematocrit, thrombocytopenia

Immune system disorders	
Not known	Other hypersensitivity/allergic reactions including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
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

The following events have also been observed during clinical trials in hypertensive patients irrespective of their causal association with the study drug: Arthralgia, asthenia, back pain, diarrhea, dizziness, headache, insomnia, libido decrease, nausea, edema, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, viral infections.

Table 3 Frequency of adverse reactions with Hydrochlorothiazide

Metabolism and nutrition disorders	
Very common:	mainly at higher doses, blood lipids increased.
Common:	hypomagnesemia, and hyperuricemia.
Rare:	hypercalcemia, hyperglycemia, glycosuria and worsening of diabetic metabolic state.
Very rare:	hypochloremic alkalosis.
Skin and subcutaneous tissue disorders	
Common:	urticaria and other forms of rash.
Rare:	photosensitivity reaction.
Very rare:	necrotizing vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
Not known	erythema multiforme
Gastrointestinal disorders	
Common:	decreased appetite, mild nausea and vomiting.
Rare:	abdominal discomfort, constipation and diarrhea.
Very rare:	pancreatitis.
Hepatobiliary disorders	
Rare:	cholestasis or jaundice.
Vascular disorders	
Common:	orthostatic hypotension, which may be aggravated by alcohol, anesthetics or sedatives.
Cardiac disorders	
Rare:	arrhythmias.

Nervous system disorders	
Rare:	headache, dizziness, sleep disorders, depression and paresthesia.
Eye disorders	
Rare:	Visual impairment particularly in the first few weeks of treatment.
Not known:	acute angle-closure glaucoma
Blood and lymphatic system disorders	
Rare:	thrombocytopenia sometimes with purpura.
Very rare:	leucopenia, agranulocytosis, bone marrow failure and hemolytic anaemia.
Not known:	aplastic anemia
Reproductive system and breast disorders	
Common:	impotence.
Immune system disorders	
Very rare:	hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary edema.
Renal and urinary disorders	
Not known:	acute renal failure, renal disorder
General disorders and administration site conditions	
Not known	pyrexia, asthenia
Musculoskeletal and connective tissue disorders	
Not known	muscle spasms

Interactions

Valsartan

Potassium: 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.

Non-Steroidal Anti-Inflammatory Agents (NSAIDs) including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, in patients who are elderly, volume-depleted (including those on diuretic therapy), or have compromised renal function, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function. Therefore, monitoring of renal function is recommended when initiating or modifying the treatment in patients on valsartan who are taking NSAIDs concomitantly.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

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.

Hydrochlorothiazide

The following potential drug interactions may occur due to the thiazide component of Co-Diovan:

Lithium: 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.

Other anti-hypertensive drugs: Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, Angiotensin Receptor Blockers (ARBs) and Direct Renin Inhibitors (DRIs)).

Skeletal muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of skeletal muscle relaxants such as curare derivatives.

Medicinal products affecting serum potassium level: The hypokalemic effect of diuretics may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or antiarrhythmics (*see Warnings and precautions*).

Medicinal products affecting serum sodium level: The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs (*see Warnings and precautions*).

Antidiabetic agents: Thiazides may alter glucose tolerance. It may be necessary to adjust the dosage of insulin and of oral antidiabetic agents.

Digitalis glycosides: Thiazide-induced hypokalemia or hypomagnesemia may occur as unwanted effects, favouring the onset of digitalis-induced cardiac arrhythmias (*see Warnings and precautions*).

NSAIDs and Cox-2 selective inhibitors: Concomitant administration of NSAIDs (e.g. salicylic acid derivative, indomethacin) may weaken the diuretic and antihypertensive activity of the thiazide component of Co-Diovan. Concurrent hypovolemia may induce acute renal failure.

Allopurinol: Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Co-administration of thiazide diuretics (including hydrochlorothiazide) may increase the risk of adverse effects caused by amantadine.

Antineoplastic agents (e.g. cyclophosphamide, methotrexate): Concomitant use of thiazide diuretics may reduce the renal excretion of cytotoxic drugs and enhance their myelosuppressive effects.

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

Ion exchange resins: Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimize the interaction.

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

Ciclosporin: Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

Calcium salts: Concomitant use of thiazide type diuretics may lead to hypercalcemia by increasing tubular calcium reabsorption.

Diazoxide: Thiazide diuretics may enhance the hyperglycemic effect of diazoxide.

Methyldopa: There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Alcohol, barbiturates or narcotics: Concomitant administration of thiazide diuretics with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension.

Pressor amines: Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use.

Overdose

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 haemodialysis because of its strong plasma binding behaviour, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Further information

Pharmacotherapeutic group

Angiotensin II antagonists combinations (valsartan) with diuretics (hydrochlorothiazide); ATC code: C09D A03

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.

Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT₁ receptor blockade with valsartan may stimulate the unblocked AT₂ receptor, which appears to counterbalance the effect of the AT₁ receptor. Valsartan does not exhibit any partial agonist activity at the AT₁ receptor and has much (about 20,000 fold) greater affinity for the AT₁ receptor than for the AT₂ receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. No potentiation of bradykinin-related side effects should be expected. 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

($P < 0.05$). Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high affinity receptor in the renal cortex with 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 affecting mechanisms of electrolyte reabsorption: – directly increasing excretion of sodium and chloride in approximately equivalent amounts, – indirectly, diuretic action reducing plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

Pharmacokinetics

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2-4 hours. Mean absolute bioavailability for Diovan is 23%. When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48%, although from about 8 hours 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 is not distributed into tissues extensively. Valsartan is highly bound to serum protein (94 to 97%), mainly serum albumin.

Biotransformation/Metabolism

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination

Valsartan shows multiexponential decay kinetics ($t_{1/2}$ alpha < 1 hour and $t_{1/2}$ beta about 9 hours). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

The pharmacokinetics of valsartan is linear in the dose range tested. There is no change in the kinetics of valsartan on repeated administration, and little accumulation when dosed once daily. Plasma concentrations were observed to be similar in males and females.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 h). The increase in mean AUC is linear and dose proportional in the therapeutic range. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 70 % after oral administration.

Distribution

The distribution and elimination kinetics have generally been described as 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. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation

Hydrochlorothiazide is eliminated predominantly as unchanged drug.

Elimination

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. More than 95 % of the absorbed dose is excreted as unchanged compound in the urine.

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 antihypertensive effect, greater than that obtained with drug given alone, or placebo.

Special Populations

Elderly

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

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

No dose adjustment is required for patients with a Glomerular Filtration Rate (GFR) of 30 to 70 mL/min.

In patients with severe renal impairment (GFR < 30 mL/min) and patients undergoing dialysis, no data are available for Co-Diovan. 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.

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, the mean elimination half-life is almost doubled. The renal clearance of hydrochlorothiazide is also reduced to a great extent compared with the renal clearance of around 300 mL/min in patients with normal renal function. Therefore, Co-Diovan should be used with caution in patients with severe renal impairment (GFR < 30 mL/min) (*see Warnings and precautions*).

Hepatic impairment

In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan was increased approximately twofold 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, and no dose reduction is considered necessary.

However, Co-Diovan should be used with particular caution in patients with biliary obstructive disorders and severe hepatic impairment (see Warnings and precautions).

Other (Clinical studies)

Administration of valsartan to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4 to 6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the maximum reduction in blood pressure with any dose is generally attained within 2 to 4 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Initial therapy with valsartan/HCTZ combination starting with a dose of 160/12.5 mg produced significantly greater reductions in blood pressure compared to valsartan monotherapy starting with a dose of 160 mg after 4 weeks in patients with severe hypertension (sitting diastolic blood pressure 110 mmHg and systolic blood pressure 140 mmHg). In other studies, the probability of achieving systolic or diastolic blood pressure control was greater with initial combination therapy than valsartan and HCTZ monotherapy at all levels of baseline blood pressure.

Pharmaceutical precautions

Instructions for use, handling and disposal

No special requirements.

Incompatibilities

Not applicable.

Shelf-life

Co-Diovan 80/12.5mg, 160/12.5mg, 320/12.5mg and 320/25mg: 36 months

Co-Diovan 160/25mg: 24 months

Special precautions for storage

Do not store above 30°C, store in the original package.

Co-Diovan must be kept out of the reach and sight of children.

Package quantities

Co-Diovan 80/12.5mg, 160/12.5mg and 160/25mg: PVC/PE/PVDC blister packs containing 14, 28, 56, 98 or 280 tablets

Co-Diovan 320/12.5mg and 320/25mg: PVC/PVDC blister packs containing 28 tablets

Medicine schedule

Prescription Medicine

Sponsor details

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