IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0013/118/004
Case No: 2057548

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Novartis Pharmaceuticals UK Ltd

Frimley Business Park, **Frimley**, **Camberley**, **Surrey, GU16 7SR**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Co-Tareg 320 mg/12.5 mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **26/02/2009** until **31/01/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Co-Tareg 320 mg/12.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 320 mg valsartan and 12.5 mg hydrochlorothiazide

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Pink, ovaloid shaped, beveled edge, film coated tablet, imprinted (debossed) with “NVR” on one side and “HIL” on the reverse side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

Co-Tareg 320 mg/12.5 mg fixed dose-combination (valsartan 320 mg / hydrochlorothiazide 12.5 mg) is indicated in patients whose blood pressure is not adequately controlled on valsartan monotherapy.

4.2 Posology and method of administration

The recommended dose of Co-Tareg 320 mg/12.5 mg is one film-coated tablet per day. Individual dose titration with the components is recommended. When clinically appropriate direct change from monotherapy to the fixed dose combination may be considered.

Co-Tareg 320 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by valsartan 320 mg monotherapy after 4-8 weeks (see section 5.1).

The maximum antihypertensive effect of Co-Tareg 320 mg/12.5 mg is seen within 4-8 weeks.

Co-Tareg 320 mg/12.5 mg may be taken independently of a meal and should be administered with fluid.

Renal impairment
No dosage adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mL/min).

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis the dose of valsartan should not exceed 80 mg. Therefore Co-Tareg 320 mg/12.5 mg should not be used in these patients.

Elderly

Co-Tareg 320 mg/12.5 mg can be used regardless of the age of the patient.

Children and adolescents (<18 years)
Co-Tareg 320 mg/12.5 mg is not recommended for use in children below the age of 18 years due to the 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.

Pregnancy and lactation (see section 4.6).

Severe hepatic impairment, biliary cirrhosis and cholestasis.

Severe renal impairment (creatinine clearance <30 mL/min), anuria and patients undergoing dialysis.

Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

Serum electrolyte changes

Concomitant use with potassium sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase serum potassium levels (heparin, etc.) should be used with caution. Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.

Treatment with thiazide diuretics has been associated with hyponatraemia and hypochloroaemic 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.

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. Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness muscle pains or cramps, muscular weakness, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.

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-Tareg 320 mg/12.5 mg. Electrolyte and/or volume depletion should be corrected before starting treatment with Co-Tareg 320 mg/12.5 mg.

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 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-Tareg 320 mg/12.5 mg in patients with severe heart failure has not been established. Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the use of Co-Tareg 320 mg/12.5 mg may as well be associated with impairment of the renal function. Co-Tareg 320 mg/12.5 mg should not be used in these patients.

Renal impairment

No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥ 30 mL/min (see section 4.3).

Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Co-Tareg 320 mg/12.5 mg is used in patients with renal impairment.

Kidney transplantation

There is currently no experience on the safe use of Co-Tareg 320 mg/12.5 mg in patients who have recently undergone kidney transplantation.

Renal artery stenosis

Co-Tareg 320 mg/12.5 mg should not be used to treat hypertension in patients with bilateral renal artery stenosis or stenosis of the artery to a single kidney, since blood urea and serum creatinine may increase in such patients.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with Co-Tareg 320 mg/12.5 mg as their renin-angiotensin aldosterone system is affected by the primary disease.

Aortic and mitral valve stenosis, hypertrophic cardiomyopathy

Special caution is indicated when using Co-Tareg 320 mg/12.5 mg in patients with aortic or mitral stenosis, or hypertrophic cardiomyopathy.

Hepatic impairment

Co-Tareg 320 mg/12.5 mg should not be used in these patients (see section 4.2).

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Ethnic differences

Valsartan is less effective in lowering blood pressure in black patients than in non blacks, possibly because of the higher prevalence of low renin levels in the black hypertensive population.

Other metabolic disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides, and uric acid.

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor blocking agents.

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

4.5 Interaction with other medicinal products and other forms of interaction

Other antihypertensive agents: Co-Tareg 320 mg/12.5 mg may increase the hypotensive effect of other antihypertensive agents.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of lithium, ACE inhibitors and/or thiazide diuretics, including hydrochlorothiazide. There is no experience with concomitant use of valsartan and lithium. Therefore, regular monitoring of serum lithium concentrations is recommended during concurrent use of lithium and Co-Tareg 320 mg/12.5 mg.

Medicinal products that may increase potassium levels or induce hyperkalaemia: Concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products that may increase potassium levels (e.g. ACE inhibitors, heparin, cyclosporin) should be used with caution and with frequent monitoring of potassium levels (see section 4.4.)

The following potential drug interactions may occur due to the thiazide component of Co-Tareg 320 mg/12.5 mg:

Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxantia, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and salicylates) 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 (see section 4.4).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when Co-Tareg 320 mg/12.5 mg is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing medicinal products (which include some antiarrhythmics), hypokalaemia being a predisposing factor to 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 intra venous (i.v.)

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effect favoring the onset of digitalis-induced cardiac arrhythmias.

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

Antidiabetic medicinal products (insulin and oral medicinal products): Dose adjustment of the antidiabetic medicinal product may be necessary.

Beta-blockers and diazoxide: Concomitant use of thiazide diuretics with betablockers 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): Dosage adjustment of uricosuric medicinal products 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 due to a decrease in gastrointestinal motility and the stomach emptying rate.

Pressor amines (e.g. noradrenaline, adrenaline): The effect of pressor amines may be decreased.

Amantadine: Thiazides, including hydrochlorothiazide, may increase the risk of undesirable 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 medicinal products and potentiate their myelosuppressive effects.

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

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): Thiazide diuretics, including hydrochlorothiazide, potentiate the action of curare derivatives.

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

Tetracyclines: Concomitant administration of tetracyclines and thiazide diuretics increases the risk for tetracycline induced increase in urea. This interaction is probably not applicable to doxycycline.

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.

4.6 Pregnancy and lactation

Angiotensin II antagonists can cause fetal injury which may be similar to the fetal effects of ACE inhibitors. In utero exposure to angiotensin converting enzyme (ACE) inhibitors given to pregnant women during the second and third trimesters has been reported to cause injury and death to the developing fetus**.**

Hydrochlorothiazide crosses the placenta and the 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.

Like other medicinal products that act directly on the renin-angiotensin-aldosterone system (RAAS), Co-Tareg 320 mg/12.5 mg should not be used during pregnancy. If pregnancy is detected during therapy, Co-Tareg 320 mg/12.5 mg should be discontinued as soon as possible.

It is not known whether valsartan is excreted in human milk. Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide is excreted in human milk. Thus it is not advisable to use Co-Tareg 320 mg/12.5 mg in lactating mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

No studies on the effect of Co-Tareg 320 mg/12.5 mg 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

Fixed-dose combination

Adverse reactions reported in clinical trials and occurring more frequently with valsartan plus hydrochlorothiazide than with placebo or from individual reports are presented below according to system organ class. Adverse reactions known to occur with each component given singly but which have not been seen in clinical trials may occur during treatment with Co-Tareg 320 mg/12.5 mg.

Adverse reactions have been ranked using the MedDRA frequency convention: very common (≥1/10); common (≥ 1/100, <1/10); uncommon (≥1/1.000, <1/100); rare (≥1/10.000, <1/1.000); very rare (<1/10.000) , not known (cannot be estimated from the available data).

Investigations

Uncommon:	Serum uric acid increased, Bilirubin and Creatinine increase, Hypokalaemia, Hyponatremia

Cardiac Disorders	
Uncommon:	Chest Pain
Rare:	Hypotension
Very rare:	Arrhythmia
Blood and lymphatic system disorders	
Very rare:	Thrombocytopenia, Anaemia
Nervous system disorders	
Uncommon:	Dizziness
Eye Disorders:	
Uncommon:	Visual disturbance
Ear and labyrinth disorders	
Rare:	Vertigo, Tinnitus
Respiratory, thoriacic and mediastinal disorders	
Uncommon:	Cough
Gastrointestinal disorders	
Common:	Diarrhoea
Uncommon:	Nausea, Dyspepsia, Abdominal pain
Renal and urinary disorders	
Uncommon:	Pollakiuria
Skin and subcutaneous tissue disorders	
Very rare:	Angiodema, Rash, Pruritus, Cutaneous vasculitis
Musculoskeletal and connective tissue disorder	
Uncommon:	Pain in extremity, ligament sprain, Arthritis
Rare:	Myalgia, Muscular weakness
Infections and infestations	
Common:	Nasopharyngitis
Uncommon:	Upper respiratory tract infections, Urinary tract infections, Viral infections, Rhinitis
General disorders and administration site conditions	
Common:	Fatigue
Rare:	Hyperhydrosis
Very rare:	Hemorrhage, Oedema, Alopecia
Immune system disorders	
Very rare:	Hypersensitivity and allergic reactions, Serum sickness

Additional information on individual components:

Undesirable effects previously reported with one of the individual components may be potential undesirable effects with Co-Tareg 320 mg/12.5 mg, even if not observed in clinical trials with this medicinal product.

Valsartan

Uncommon: asthenia, back pain, conjunctivitis, depression, epistaxis, insomnia, muscle cramps, sinusitis, vertigo.

Rare: neuralgia

Very rare: arthralgia, gastoenteritis

Post-marketing data revealed rare cases of angioedema, rash, pruritus and other allergic reactions including serum sickness, and vasculitis, very rare cases of impaired renal function; in some cases pre-existing renal impairment was temporarily intensified.

Uncommon elevations of liver function values were reported in patients treated with valsartan.

Hydrochlorothiazide

The following adverse reactions have been reported in patients treated with thiazide diuretics alone, including hydrochlorothiazide, frequently at higher doses than those contained in Co-Tareg.

Common: urticaria and other forms of rash, loss of appetite, mild nausea and vomiting, postural hypotension, impotence.

Rare: photosensitisation, constipation, diarrhoea, gastrointestinal discomfort, intrahepatic cholestasis or jaundice, cardiac arrhythmias, headache, dizziness or light-headedness, sleep disturbances, depression, paraesthesias, disturbances of vision, thrombocytopenia sometimes with purpura.

Very rare: necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, pancreatitis, leucopenia, agranulocytosis, bone marrow depression, haemolytic anaemia, hypersensitivity reactions, respiratory distress including pneumonitis and pulmonary oedema.

Electrolytes and metabolic disorders: see section 4.4.

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.

The patient should be given a sufficient amount of activated charcoal. 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 can be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Valsartan

Valsartan is an orally active, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20,000 fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

Valsartan does not inhibit ACE, also known as kininase II, which converts Ang I to Ang II and degrades bradykinin. No potentiation of bradykinin related undesirable 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 with 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.

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 4-6 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 4-8 weeks and is sustained during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.

Hydrochlorothiazide

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 as the primary binding site for the thiazide diuretic action and inhibition of NaCl (Sodium chloride) transport in the distal convoluted tubule. The mechanism 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 by increasing sodium and chloride excretion to an approximately equal extent, and indirectly by their 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.

Valsartan / hydrochlorothiazide

A multicentre, randomised double blind, active controlled, parallel group trial has shown a normalisation of blood pressure (defined as trough sitting diastolic BP < 90 mmHg) with Co-Tareg 80 mg/12.5 mg in 42.6 % of the patients (non-responders to hydrochlorothiazide) at the end of the trial.

A second randomised double blind, active controlled, parallel group trial has shown that the fixed combination of valsartan 160 mg with HCTZ (Hydrochlorothiazide) 12.5 mg or 25 mg improved blood pressure control in a higher proportion of patients than monotherapy with valsartan 160 mg. Furthermore, the fixed combination with HCTZ 25 mg was significantly more effective than the fixed combination with the lower dose of HCTZ. The following responder rates were observed: valsartan 160 mg: 49 %; valsartan 160 mg + HCTZ 12.5 mg: 61.7 %; valsartan 160 mg + HCTZ 25 mg: 68 %.

Another randomised double blind, active controlled, parallel group trial in patients not adequately controlled with valsartan monotherapy 320 mg has shown that the fixed combinations of valsartan/HCTZ 320 mg/25 mg and 320 mg/12.5 mg were more effective than valsartan 320 mg. The following responder rates were observed: valsartan 320 mg: 52.7 %; valsartan 320 mg + HCTZ 12.5 mg: 68.8 %; valsartan 320 mg + HCTZ 25 mg: 74.9 %. An additional analysis showed that more severe patients (MSDBP at baseline ≥ 100mmHg) achieved higher responder rates with valsartan 320 mg/HCTZ 25 mg (69.2%) compared to valsartan 320 mg/HCTZ 12.5 mg (56.1%).

A randomised double blind multifactorial trial compared various dosage combinations of valsartan and HCTZ to their respective components and placebo. The following MSSBP/MSDBP reductions were observed: -24.7/16.6 mmHg for valsartan/HCTZ 320 mg/25 mg; -21.7/-15.0 mmHg for valsartan/HCTZ 320 mg/12.5 mg; -20.3/-15.2 mmHg for valsartan/HCTZ 160 mg/12.5 mg.

Dose-dependent hypokalaemia occurred in controlled clinical studies with valsartan + HCTZ. Hypokalaemia occurred more frequently in patients given 25 mg HCTZ than in those given 12.5 mg HCTZ.

Dose-dependent orthostatic reactions were reported in < 1 % of patients given a combination of valsartan + HCTZ. A dose-dependent increase in the frequency of “dizziness” was reported in patients treated with doses ranging from valsartan 80 mg + HCTZ 12.5 mg to valsartan 160 mg + HCTZ 25 mg. In a non-controlled study in which Co-Tareg 160 mg/25 mg was given for 4 weeks to patients who had not been adequately treated with valsartan 160 mg and HCTZ 12.5 mg, total cholesterol rose from 209 to 220 mg/dl.

Beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity are currently unknown. Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity. Studies are ongoing to investigate the effects of valsartan and valsartan in combination with hydrochlorothiazide on cardiovascular mortality and morbidity.

5.2 Pharmacokinetic properties

Valsartan

Absorption of valsartan after oral administration is rapid, although the amount absorbed varies widely. Mean absolute bioavailability for valsartan is 23 %. Valsartan shows multiexponential decay kinetics ($t_{1/2}\alpha$ <1h and $t_{1/2}$ ß about 9 h).

The pharmacokinetics of valsartan are 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 similar in males and females.

Valsartan is highly bound to serum protein (94-97 %), mainly serum albumin. Steady-state volume of distribution is about 17 Litres. Plasma clearance is about 2 L/h. Valsartan is mainly eliminated as unchanged compound in the bile and in the urine. At normal glomerular filtration rate (120 mL/min), renal clearance accounts for about 30 % of total plasma clearance. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10 % of the valsartan AUC). This metabolite is pharmacologically inactive. After oral dosing of valsartan 83 % is excreted in the faeces and 13 % in the urine, mainly as unchanged compound.

When valsartan is given with food, the area under the plasma concentration curve (AUC) of valsartan is reduced by 48 %, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not accompanied by a clinically significant reduction in the therapeutic effect.

Hydrochlorothiazide

The absorption of hydrochlorothiazide, after an oral dose, is rapid (t_{max} about 2 h), with similar absorption characteristics for both suspension and tablet formulations. The distribution and elimination kinetics have generally been described by a bi-exponential decay function, with a terminal half-life of 6-15 h.

The increase in mean AUC is linear and dose proportional in the therapeutic range. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. 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 1.8 times the level in plasma.

Absolute bioavailability of hydrochlorothiazide is 60-80 % after oral administration, with >95 % of the absorbed dose being excreted as unchanged compound in the urine.

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.

Valsartan / hydrochlorothiazide

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 anti-hypertensive effect, greater than that obtained with either medicinal product given alone, or with 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

At the recommended dose of Co-Tareg 320 mg/12.5 mg 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 in patients undergoing dialysis no data are available for Co-Tareg.

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 (see section 4.3).

Hepatic impairment

In a pharmacokinetics trial in patients with mild (n=6) to moderate (n=5) hepatic dysfunction, exposure to valsartan has shown an approximately 2-fold increase in AUC and C_{max} values compared with healthy volunteers. Therefore, Co-Tareg 320 mg/12.5 mg should not be used in these patients (see section 4.2). There is no data available on the use of valsartan in patients with severe hepatic dysfunction (see section 4.3).

Hepatic disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

The potential toxicity of the valsartan + hydrochlorothiazide combination after oral administration was investigated in rats and marmosets in studies lasting up to six months. No findings emerged that would exclude the use of therapeutic doses in man.

The changes produced by the combination in the chronic toxicity studies are most likely to have been caused by the valsartan component.

The toxicological target organ was the kidney, the reaction being more marked in the marmoset than the rat. The combination led to kidney damage (nephropathy with tubular basophilia, rises in plasma urea, plasma creatinine and serum potassium, increases in urine volume and urinary electrolytes from 30 mg/kg/d valsartan + 9 mg/kg/d hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics.

High doses of the valsartan + hydrochlorothiazide combination caused falls in red blood cell indices (red cell count, haemoglobin, haematocrit, from 100 + 31 mg/kg/d in rats and 30 + 9 mg/kg/d in marmosets).

In marmosets, damage was observed in the gastric mucosa (from 30 + 9 mg/kg/d).

The combination also led in the kidney to hyperplasia of the afferent aterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets).

The above mentioned effects appear to be due to the pharmacological effects of high valsartan doses (blockade of angiotensin II-induced inhibition of renin release, with stimulation of the renin-producing cells) and also occur with ACE inhibitors. These findings appear to have no relevance to the use of therapeutic doses of valsartan in humans.

The valsartan + hydrochlorothiazide combination was not tested for mutagenicity, chromosomal breakage or carcinogenicity, since there is no evidence of interaction between the two substances. However, these tests were performed separately with valsartan and hydrochlorothiazide, and produced no evidence of mutagenicity, chromosomal breakage or carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Silica. Colloidal anhydrous
Crospovidone
Magnesium stearate

Coating:
Hypromellose
Macrogol 4000
Talc
Titanium dioxide (E171)
Black iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30° C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/ PVDC/Alu blisters.
7, 14, 28, 56, 98, 280 film-coated tablets

PVC/PVDC/Alu perforated unit dose blisters
56x1, 98x1, 280x1 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Ltd.
Frimley Business Park
Frimley
Camberley
Surrey
GU 16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0013/118/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st February 2008

10 DATE OF REVISION OF THE TEXT

February 2008