1. NAME OF THE MEDICINAL PRODUCT

co-cinfaval 160 mg/12.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.

Excipients with known effect:
This medicinal product contains 2.3 mg of lactose, 18.5 mg of sorbitol and 7.67 mg of pregelatinised corn starch.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Reddish, cylindrical, biconvex, coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential arterial hypertension in adults.

The fixed-dose combination of valsartan and hydrochlorothiazide is indicated for patients in whom adequate blood pressure control is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

Posology

The recommended dose of valsartan/hydrochlorothiazide 160 mg/12.5 mg is one film-coated tablet per day. Individually adjusting the dose of the individual components is recommended. In each case, the individual component must be individually adjusted until the next dose in order to reduce the risk of hypotension and other adverse effects.
When it is deemed clinically appropriate, a direct change from monotherapy to fixed-dose combination may be considered for patients in whom adequate blood pressure control is not achieved with valsartan or hydrochlorothiazide monotherapy, provided that the recommended sequence for adjusting the individual dose of the individual components is followed.

The clinical response to valsartan/hydrochlorothiazide must be evaluated after starting the treatment, and if control of the patient's blood pressure is not achieved, the dose may be increased by raising the quantity of one of the components up to the maximum dose of 320 mg/25 mg of valsartan/hydrochlorothiazide.

The antihypertensive effect is significantly present after 2 weeks.
In most patients, the maximum effects are seen after 4 weeks. However, some patients may need 4-8 weeks of treatment. This should be taken into consideration when the dose is adjusted.

Method of administration
valsartan/hydrochlorothiazide can be taken with or without food and must be administered with water.

Special populations

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance ≥30 ml/min). Due to the component hydrochlorothiazide, valsartan/hydrochlorothiazide is contraindicated in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).

Hepatic impairment
In patients with mild to moderate Hepatic impairment without cholestasis, the valsartan dose should not exceed 80 mg (see section 4.4). valsartan/hydrochlorothiazide is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
It is not necessary to adjust the dose in elderly patients.

Paediatric population
The use of valsartan/hydrochlorothiazide in children under 18 years of age is not recommended as its safety and efficacy have not yet been established.

4.3 Contraindications

- Hypersensitivity to valsartan, hydrochlorothiazide, other drugs derived from sulphonamide or any of the excipients.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia or symptomatic hyperuricaemia.

4.4 Special warnings and precautions for use

Serum electrolyte changes
Valsartan
Concomitant use of potassium supplements, potassium-sparing diuretics, salt substitutes that contain potassium or other agents that may increase potassium levels (heparin, etc.) is not recommended. Potassium levels must be suitably monitored.

Hydrochlorothiazide
Cases of hypokalaemia have been documented during treatments 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 lead to hypomagnesemia. The excretion of calcium decreases with thiazide diuretics, which may lead to hypercalcaemia.
Serum electrolytes must be tested periodically at appropriate intervals in patients receiving treatment with diuretics.

Patients with sodium and/or volume depletion
Patients who receive thiazide diuretics, including hydrochlorothiazide, should be observed for the appearance of clinical signs of fluid or electrolyte imbalance.

Patients with severe sodium and/or volume depletion, such as those receiving high doses of diuretics, may, in rare cases, experience symptomatic hypotension after starting treatment with valsartan/hydrochlorothiazide. Sodium and/or volume depletion should be corrected before commencing treatment with valsartan/hydrochlorothiazide.

Patients with serious chronic heart failure or other clinical situations with renin-angiotensin-aldosterone system stimulation
In patients whose renal function could be dependent on the activity of the renin-angiotensin-aldosterone system (for example, patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and, rarely, with acute renal failure. The use of valsartan/hydrochlorothiazide in patients with severe chronic heart failure has not been established.
Therefore, due to the inhibition of the renin-angiotensin-aldosterone system, it cannot be excluded that the use of valsartan/hydrochlorothiazide may also be associated with impairment of the renal function. valsartan/hydrochlorothiazide should not be used with 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 because blood urea and serum creatinine levels may increase in these patients.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with valsartan/hydrochlorothiazide as the renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all vasodilators, special caution is recommended in patients with aortic or mitral stenosis, or with hypertrophic obstructive cardiomyopathy (HOCM).

Renal impairment In patients with renal failure with creatinine clearance ≥30 ml/min no dose adjustment is required (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid is recommended when valsartan/hydrochlorothiazide is used in patients with renal impairment.

Kidney transplantation There is no current experience on the safety of using valsartan/hydrochlorothiazide in patients who have recently undergone a kidney transplantation.

Hepatic impairment In patients with mild or moderate hepatic impairment without cholestasis, valsartan/hydrochlorothiazide should be used with caution (see sections 4.2 and 5.2).

Systemic lupus erythematous
It has been observed that thiazide diuretics, including hydrochlorothiazide, exacerbate or activate systemic lupus erythematous.

Other metabolic alterations
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients, insulin or oral hypoglycaemiant drug doses may need to be adjusted.
Thiazides may reduce the excretion of calcium in urine, causing a slight intermittent increase in the calcium concentration in serum in absence of known alterations in calcium metabolism. Marked hypercalcaemia may be indicative of underlying hyperparathyroidism. Thiazides treatment should be discontinued before conducting parathyroid function tests.

Photosensitivity
Cases of photosensitive reactions have been reported with thiazide diuretics (see section 4.8). If photosensitive reactions appear during treatment, suspending the treatment is recommended. If it is considered necessary to reintroduce the diuretic, areas exposed to the sun or to artificial UVA rays should be protected.

Pregnancy
Treatment with angiotensin II receptor antagonists (AIIRAs) should not be started during pregnancy. Unless it is considered essential to continue treatment with AIIRAs, patients planning to get pregnant must change to an alternative antihypertensive treatment with a known safety profile for use during

pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and an alternative treatment started if required (see sections 4.3 and 4.6).

General
Caution should be taken in patients with prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergies or asthma.

Important information about some of the ingredients of co-cinfaval
This medicinal product contains lactose. Patients with hereditary intolerance to galactose, Lapp lactase deficiency (deficiency seen in some populations in Lapland) or glucose or galactose absorption problems must not take this medicine.
This medicine contains sorbitol. Patients with hereditary intolerance to fructose should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to valsartan and hydrochlorothiazide

Concomitant use not recommended
Lithium
Reversible increases have been observed in serum lithium concentrations and in its toxic effects during concomitant use with ACE inhibitors and thiazides, including hydrochlorothiazide. Due to the lack of experience in the concomitant use of valsartan and lithium, this combination is not recommended. If the combination is necessary, exhaustive 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 (such as ACE inhibitors, beta-blockers, calcium channel blockers).

Pressor amines (such as noradrenaline, adrenaline)
A possible reduction in the response to pressor amines is insufficient to preclude their use.

Non-steroidal anti-inflammatory drugs (NSAIDs), including COX-2 selective inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDS
NSAIDs can attenuate the antihypertensive effect of angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Moreover, concomitant use of valsartan/hydrochlorothiazide and NSAIDs could lead to worsening of renal function and increase in serum potassium. Therefore, renal function monitoring is recommended at the start of treatment, as well as adequate patient hydration.

Interactions related to valsartan

Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substituents containing potassium and other substances that may increase potassium levels.
If it is necessary to use a medicine that affects potassium levels in combination with valsartan, monitoring of serum potassium levels is recommended.

No interaction
In pharmacological interaction studies with valsartan, no clinically significant interactions with valsartan were found, nor with the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine and glibenclamide. Digoxin and

indomethacin could interact with the hydrochlorothiazide component in valsartan/hydrochlorothiazide (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution
Drugs associated with potassium loss and hypokalaemia (such as kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and its derivatives)
Serum potassium levels should be monitored if these drugs must be prescribed in combination with valsartan/hydrochlorothiazide. These drugs may enhance the effect of hydrochlorothiazide of serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
- Class Ia antiarrhythmics (such as quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (such as amyodarone, sotalol, dofetilide, ibutilide)
- Certain antipsychotics (such as thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (such as bepridil, cisapride, diphemanil, erythromycin i.v., halofantrine, ketanserin, mizolastine, pentamidine, sparfloxacin, terfenadine, vincamine i.v.)

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

Digitalic glycosides
Hypokalaemia or hypomagnesemia caused by thiazides can be observed as undesirable side effects, prompting the appearance of cardiac arrhythmias caused by digitalic glycosides.

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

Antidiabetic agents (oral agents and insulin)
Thiazide treatment may affect glucose tolerance. It may be necessary to adjust the dose of antidiabetic medicine.
Metformin should be used with caution due to the risk of lactic acidosis induced by a possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide
The 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.

Medicines used to treat gout (probenecid, sulfinpyrazone and allopurinol)
It may be necessary to adjust the dose of uricosuric medication as hydrochlorothiazide may increase levels of uric acid. The dose of probenecid or sulfinpyrazone may need to be increased. Concomitant administration of thiazide diuretics, including hydrochlorothiazide, may increase the rate of hypersensitivity reactions to allopurinol.

Anticholinergic agents (i.e. atropine, biperiden)
The bioavailability of thiazide-type diuretics may increase with the use of anticholinergic agents, apparently due to the decreased gastrointestinal motility and stomach emptying rate.

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

Cholestyramine and colestipol resins
Absorption of thiazide diuretics, including hydrochlorothiazide, is impaired when ion exchange resins are present.

Cytotoxic agents (i.e. cyclophosphamide and methotrexate)
Thiazides, including hydrochlorothiazide, may reduce the rate of renal excretion of cytotoxic agents and enhance their myelosuppressive effects.

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

Cyclosporine
Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and of gout-type complications.

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

Methyldopa
Isolated cases of haemolytic anaemia have been reported in patients who received concomitant treatment with methyldopa and hydrochlorothiazide.

Carbamazepine
Patients receiving hydrochlorothiazide and carbamazepine concomitantly may develop hyponatraemia. Therefore, these patients must be warned of the possibility of hyponatraemic reactions and monitored accordingly.

Iodinated contrasts
In the event of dehydration caused by diuretics, the risk of acute renal failure increases, especially with high doses of iodinated products. Patients much be rehydrated before the administration.

4.6 Pregnancy and lactation

Pregnancy

Valsartan

Use of Angiotensin II Receptor Antagonist (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (see Section 4.3 and 4.4).

The epidemiological evidence on the risk of teratogenicity after exposure to ACE inhibitors during the first trimester of pregnancy was not conclusive; however, a small increase in risk cannot be excluded. Despite having no specific epidemiological data on the risk of administering AIIRAs during pregnancy, there may be similar risks for this type of medicines. Unless it is considered essential to continue treatment with AIIRAs, patients planning to get pregnant must change to an alternative antihypertensive treatment with a known safety profile for use during pregnancy. When pregnancy is diagnosed, treatment with AIIRAs must be stopped immediately and an alternative treatment started if required.

Exposure to AIIRAs in the second and third trimester is known to cause human fetotoxicity (decrease in renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypertension, hyperpotassaemia), (see section 5.3).
If there is AIIRAs exposure from the second trimester of pregnancy, an ultrasound test is recommended to check renal function and the cranium.
Infants whose mothers have been treated with AIIRAs must be carefully monitored in case hypotension occurs (see sections 4.3 and 4.4).

Hydrochlorothiazide

There is limited experience on the use of hydrochlorothiazide during pregnancy, especially during the first trimester. Studies on animals are insufficient. Hydrochlorothiazide crosses the placenta. Based on hydrochlorothiazide's pharmacological action mechanism, its use during the second and third trimester of pregnancy may compromise foetal placental perfusion and may cause foetal and neonatal effects such as icterus, disturbance of electrolyte balance and thrombocytopaenia.

Lactation There is no information relating to the use of valsartan while breast-feeding. Hydrochlorothiazide is excreted in human breast milk. Therefore, administration of valsartan/hydrochlorothiazide is not recommended during such time. It is preferable to change to a treatment with a more well-known safety profile for breast-feeding, especially while nursing a newborn or preterm infant.

4.7 Effects on the ability to drive and use machines

No studies have been made of the effects of valsartan/hydrochlorothiazide upon the ability to drive and use machines. When driving or using machinery, take into account that dizziness or weariness may sometimes occur.

4.8 Undesirable effects

Below, the undesirable effects, classified by organ systems, most frequently reported in clinical trials or laboratory findings with valsartan plus hydrochlorothiazide compared to a placebo, or from individual post-marketing case studies, are shown. 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.

The undesirable effects have been classified by frequency, with the most frequent first, according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/1,000 to < 1/1,000); very rare(< 1/10,000), not known frequency (cannot be estimated from the available data). Within each frequency grouping, adverse effects are presented in order of decreasing seriousness.

Table 1. Frequency of undesirable effects with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders	
Uncommon	Dehydration
Nervous system disorders	
Very rare	Dizziness
Uncommon	Paraesthesia
Not known frequency	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 frequency	Not cardiogenic pulmonary oedema
Gastrointestinal disorders	
Very rare	Diarrhoea
Musculoskeletal and connective tissue disorders	
Uncommon	Myalgia
Very rare	Arthralgia
Renal and urinary disorders	

Not known frequency	Impaired renal function
General disorders and administration site conditions	
Uncommon	Fatigue
Investigations	
Not known frequency	Increase in serum uric acid levels, increase in serum creatinine and bilirubin, hypokalaemia, hyponatraemia, rise in blood urea nitrogen level, neutropenia

Additional information on the individual components

The undesirable effects reported previously with the individual administration of one of the components may also be potential undesirable effects of valsartan/hydrochlorothiazide, despite the fact that they have not been seen in clinical trials or during the post-marketing period.

Table 2. Frequency of undesirable effects with valsartan

Blood and lymphatic system disorders	
Not known frequency	decrease in haemoglobin, decrease in haematocrit, thrombocytopaenia
Immune system disorders	
Not known frequency	Other hypersensitivity/allergic reactions, including serum sickness
Metabolism and nutrition disorders	
Not known frequency	Increase in serum potassium levels
Ear and labyrinth disorders	
Uncommon	Vertigo
Vascular disorders	
Not known frequency	Vasculitis
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepatobiliary disorders	
Not known frequency	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Not known frequency	Angioedema, rash, pruritus
Renal and urinary disorders	
Not known frequency	Renal failure.

Table 3. Frequency of undesirable effects with hydrochlorothiazide

Hydrochlorothiazide has been widely prescribed for many years, often at doses that are higher than those administered in valsartan/hydrochlorothiazide. The following undesirable effects have been reported in patients treated with monotherapy thiazide diuretics, including hydrochlorothiazide:

Blood and lymphatic system disorders	
Rare	Thrombocytopenia, sometimes with purpura
Very rare	Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow suppression
Immune system disorders	
Very rare	Hypersensitivity reactions
Psychiatric disorders	
Rare	Depression, sleep disturbances
Nervous system disorders	
Rare	Headache
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
Skin and subcutaneous tissue disorders	
Common	Urticaria and other forms of rash
Rare	Photosensitisation
Very rare	Necrotizing vasculitis and toxic epidermal necrolysis, reactions similar to cutaneous lupus erythematosus, reactivation of cutaneous lupus erythematosus
Reproductive system and breast disorders	
Common	Impotence

4.9 Overdose

Symptoms
An overdose of valsartan may result in marked hypotension that can cause a low level of consciousness, circulatory collapse and/or shock. Also, the following signs and symptoms may be observed 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, and 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 haemodialysis, due to 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 with diuretics, valsartan and diuretics; ATC code: C09D A03.

Valsartan/hydrochlorothiazide

In a randomised, double-blind active control trial on patients not adequately controlled with 12.5 mg of hydrochlorothiazide, significantly greater reductions were found of the average systolic/diastolic BP with the combination of 160/12.5 mg of valsartan/hydrochlorothiazide (12.4/7.5 mmHg) compared to 25 mg of hydrochlorothiazide (5.6/2.1 mmHg). Moreover, a significantly higher percentage of patients responded (BP <140/90 mmHg or a reduction of SBP ≥20 mmHg or a reduction of DBP ≥10 mmHg) with 160/12.5 mg of valsartan/hydrochlorothiazide (50%) compared to 25 mg of hydrochlorothiazide (25%)

In a randomised, double-blind active control trial on patients not adequately controlled with 160 mg of valsartan, significantly greater reductions were found of the average systolic/diastolic BP with the combination of 160/25 mg of valsartan/hydrochlorothiazide (14.6/11.9 mmHg) and 160/12.5 mg of valsartan/hydrochlorothiazide (12.4/10.4 mmHg) compared to 160 mg of valsartan (8.7/8.8 mmHg).

The difference in the BP reductions between the 160/25 mg dose and the 160/12.5 mg dose was also statistically significant. Moreover, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or a reduction of ≥10 mmHg) with 160/25 mg (68%) and 160/12.5 mg (62%) of valsartan/hydrochlorothiazide compared to 160 mg of valsartan (49%).

In a randomised, double-blind placebo-controlled factorial-designed trial that compared several doses of valsartan/hydrochlorothiazide combinations with their respective components, significantly greater reductions were seen of the average systolic/diastolic BP with the combination of 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) of valsartan/hydrochlorothiazide compared with the placebo (1.9/4.1 mmHg) and the respective monotherapy options, such as 12.5 mg of hydrochlorothiazide (7.3/7.2 mmHg), 25 mg of hydrochlorothiazide (12.7/9.3 mmHg) and 160 mg of valsartan (12.1/9.4 mmHg). Moreover, a significantly higher percentage of patients responded (diastolic BP <90 mmHg or a reduction of ≥10 mmHg) with 160/25 mg of valsartan/hydrochlorothiazide (81%) and 160/12.5 mg of valsartan/hydrochlorothiazide (76%) compared with the placebo (29%) and the respective monotherapy options, such as 12.5 mg of hydrochlorothiazide (41%), 25 mg of hydrochlorothiazide (54%) and 160 mg of valsartan (59%).

In controlled clinical trials with valsartan + hydrochlorothiazide, dose-dependent reductions were found in serum potassium levels. The serum potassium reduction took place more often in patients who received 25 mg of hydrochlorothiazide than in those who received 12.5 mg of hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide, the lowering effect of hydrochlorothiazide on potassium levels was attenuated by the potassium-sparing effect of valsartan.

The beneficial effects of valsartan in combination with hydrochlorothiazide on cardiovascular mortality or morbidity are currently unknown.
Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality or morbidity.

Valsartan
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT_1 subtype receptor, which is responsible for the known action mechanisms of angiotensin II. High Ang II levels after AT_1 receptor blocking with valsartan may stimulate the unblocked AT_2 receptor, which appears to compensate the effect of the AT_1 receptor. Valsartan does not show any partial agonist activity on the AT_1 receptor and shows a much greater affinity (approximately 20,000 times higher) for the AT_1 receptor than for the AT_2 receptor. Valsartan does not bind to or block other hormone receptors or ion channels known for their important intervention in cardiovascular regulation.

Valsartan does not inhibit the ACE (also known as kininase II) that transforms Ang I into Ang II and degrades bradykinin. As there is no effect on the ACE and the bradykinin and P substance are not boosted, it is unlikely that the angiotensin II antagonists are associated with coughing. In the clinical trials that compared valsartan with an ACE inhibitor, dry cough incidence was significantly lower ($P < 0.05$) in patients treated with valsartan than in patients treated with an ACE inhibitor (2.6% versus 7.9% respectively). In one clinical trial, in patients with a history of a dry cough during treatment with an ACE inhibitor, 19.5% of patients who received valsartan and 19.0% of patients who received a thiazide diuretic experienced coughing, compared with 68.5% of patients treated with the ACE inhibitor ($P <0.05$).

The administration of valsartan to hypertensive patients reduces blood pressure without modifying heart rate. In most patients, after being administered in a single oral dose, the onset of the antihypertensive action occurs in the first 2 hours and maximum reduction of blood pressure is reached in 4-6 hours. The antihypertensive effect persists for 24 hours after the dose. When administered in repeated doses, maximum reduction of blood pressure usually occurs between 2 - 4 weeks with all the doses and persists during prolonged treatment. If hydrochlorothiazide is added, a significant additional reduction is seen in blood pressure.

Abrupt withdrawal of valsartan has not been associated with rebound hypertension episodes or other clinical adverse events.
In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has shown a reduction in urinary excretion of albumin. The MARVAL study (*Micro Albuminuria Reduction with Valsartan*) evaluated the reduction in urinary excretion of albumin (UEA) with valsartan (80-160 mg/once per day) versus amlodipine (5-10 mg/once per day), in 332 patients with type 2 diabetes (average age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55,4 µg/min), normal or raised blood pressure and preserved renal function (creatinine in blood < 120 µmol/l). At 24 weeks, the UEA reduced ($p < 0.001$) by 42% (–24.2 µg/min; CI of 95%: –40.4 to –19.1) with valsartan and approximately by 3% (–1.7 µg/min; CI of 95%: –5.6 to 14.9) with amlodipine despite similar reduction rates in blood pressure in both groups. The *Diovan Reduction of Proteinuria* (DROP) study also examined the efficacy of valsartan in reducing the UEA in 391 hypertensive patients (BP = 150/88 mmHg) with type 2 diabetes, albuminuria (mean = 102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). The patients were randomised to 1 of 3 valsartan posologies (160, 320 and 640 mg/once per day) and were treated for 30 weeks. The purpose of the study was to determine the optimum dose of valsartan to reduce the UEA in hypertensive patients with type II diabetes. At 30 weeks, the percentage change in UEA reduced significantly by 36% from the baseline with valsartan 160 mg (CI of 95%: 22 to 47%), and by 44% with valsartan 320 mg (CI of 95%: 31 to 54%). The conclusion was that 160-320 mg of valsartan produced clinically significant reductions in UEA in hypertensive patients with type 2 diabetes.-{}-

Hydrochlorothiazide
The action site of thiazide diuretics is primarily the distal convoluted tubule of the kidneys. It has been shown that there is a receptor in the renal cortex with an elevated affinity that is the primary binding site for the action of thiazide diuretics and for the inhibition of the transportation of NaCl in the distal convoluted tubule. The mechanism of action of thiazides consists of the inhibition of the Na^+Cl^- co-transport system, perhaps competing for the Cl^-'s site, which affects the mechanisms of reabsorption of electrolytes: directly increasing the excretion of sodium and chloride in almost equal amounts, and indirectly, through the diuretic action, reducing the plasma volume and increasing the activity of the plasma renin, the secretion of aldosterone, the urinary loss of potassium and decreasing the potassium in plasma. The renin-aldosterone bond is mediated by angiotensin II so that, when concomitantly administered with valsartan, the reduction of serum potassium is less pronounced than that seen with hydrochlorothiazide monotherapy.

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide
The systemic availability of hydrochlorothiazide decreases by approximately 30% when valsartan was also added. The kinetics of valsartan is not notably modified with the concomitant administration of hydrochlorothiazide. This interaction does not affect the combined use of valsartan and hydrochlorothiazide, as the controlled clinical trials have shown an evident antihypertensive effect, greater than that obtained with each ingredient alone, or with the administration of a placebo.

Valsartan
Absorption
After oral administration of valsartan in monotherapy, maximum plasma concentrations of valsartan are reached in 2-4 hours. The mean absolute bioavailability is 23%. Food reduced the exposure (measured by the UAC) of valsartan by approximately 40% and the maximum plasma concentration (C_{max}) by approximately 50%. However, from 8 hours post-administration, plasma concentrations of valsartan in groups receiving the medicine in fasting and non-fasting conditions are similar. However, this UAC reduction is not associated with a clinically significant reduction of the therapeutic effect and therefore valsartan may be administered with or without food.

Distribution
The distribution volume at a steady state after intravenous administration is some 17 litres, indicating that there is not much distribution of valsartan to tissues. Valsartan shows a high serum protein binding (94-97%), mainly to serum albumin.

Biotransformation
Valsartan does not biotransform much, as only approximately 20% of the dose is recovered in the form of metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of valsartan UAC). This metabolite is pharmacologically inactive.

Elimination
Elimination kinetics of valsartan are multiexponential ($t_{½\alpha}$ < 1 h and $t_{½\beta}$ approximately 9 hours). Valsartan is mainly eliminated in stools (approximately 83% of the dose) and in urine (approximately 13% of the dose), mainly as an unchanged compound. After intravenous administration, the plasma clearance is 2 L/h approximately and renal clearance is 0.62 L/h (approximately 30% of the total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
Absorption
Absorption of hydrochlorothiazide after an oral dose is fast (t_{max} of approx. 2 hours), and the formulations in suspension and in tablets show similar absorption characteristics. After oral administration, the mean absolute oral bioavailability of hydrochlorothiazide is 60 to 80%. It has been observed that concomitant administration with food may increase or decrease the systemic availability of hydrochlorothiazide when compared to its administration in fasting conditions. The extent of these effects is small and has minimal clinical importance. The increase of the mean AUC is linear and proportional to the dose within the therapeutic range. The kinetics of hydrochlorothiazide is not modified through repeated administration and the accumulation is minimal when administered once a day.

Distribution
The elimination and distribution kinetics have generally been described with a bi-exponential function. The apparent volume of distribution is 4-8 l/kg.
The circulating hydrochlorothiazide bonds to serum proteins (40-70%), mainly to serum albumin. Hydrochlorothiazide also accumulates in the erythrocytes at approximately 1.8 times the plasma level.

Elimination
In relation to hydrochlorothiazide, >95% of the dose absorbed is excreted as an unchanged compound in urine. Renal clearance consists of passive filtration and active secretion in the renal tubule. The terminal half-life is 6.15 h.

Special populations

Elderly patients
Some elderly people show a somewhat higher systemic exposure to valsartan than young individuals; however, this difference has not been shown to be clinically significant.
The limited results available suggest that systemic clearance of hydrochlorothiazide drops in both healthy and hypertensive elderly patients when compared to young healthy volunteers.

Renal impairment No dose adjustment is required in patients with creatinine clearance 30-70 ml/min at the recommended dose of valsartan/hydrochlorothiazide.

No data are available for valsartan/hydrochlorothiazide administered to patients with severe renal impairment (creatinine clearance < 30 ml/min) or those undergoing dialysis. Valsartan shows a high plasma protein binding rate and cannot be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

Renal clearance of hydrochlorothiazide consists of passive filtration and active secretion in the renal tubule. As expected for a compound that is almost exclusively cleared through the kidney, renal function has a strong effect on the kinetics of hydrochlorothiazide (see section 4.3).

Hepatic impairment

In a pharmacokinetic study in patients with mild (n=6) and moderate liver dysfunction (n=5), exposure to valsartan was approximately double that of healthy volunteers. No data are available on the use of valsartan in patients with severe liver dysfunction (see section 4.3). Liver disease does not significantly affect the pharmacokinetics of hydrochlorothiazide.

5.3 Preclinical safety data

Research was conducted on the potential toxicity of the combination of valsartan and hydrochlorothiazide taken orally by rats and marmosets in studies lasting up to six months. No findings were detected that excluded their use at therapeutic doses in humans.

The changes produced by the combination in chronic toxicity studies appear to be caused by valsartan. The target toxicological organ was the kidney, with a more significant reaction in marmosets than in rats. The combination led to kidney damage (nephropathy with tubular basophilia, an increase of plasma urea, plasma creatinine and plasma potassium, an increase in urine volume and of urinary electrolytes from doses of 30 mg/kg/day of valsartan and 9 mg/kg/day of hydrochlorothiazide, in rats, and 10 mg/kg/day of valsartan and 3 mg/kg/day of hydrochlorothiazide in marmosets), probably due to altered renal haemodynamics. These doses in rats represent, respectively, 0.9 and 3.5 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. These doses in marmosets represent, respectively, 0.3 and 1.2 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. (The calculations take an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide in patients weighing 60 kg).

High doses of the combination of valsartan and hydrochlorothiazide caused decreases in the erythrocyte figures (erythrocyte count, haemoglobin and haematocrit, starting at 100 + 31 mg/kg/day in rats and 30 + 9 mg/kg/day in marmosets). These doses in rats represent, respectively, 3.0 and 12 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. These doses in marmosets represent, respectively, 0.9 and 3.5 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. (The calculations take an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide in patients weighing 60 kg).

In marmosets, damage of the gastric mucosa was observed (with doses greater than 30 + 9 mg/kg/d). The combination also led to hyperplasia of the renal afferent arterioles (with doses of 600 + 188 mg/kg/d in rats, and starting at 30 + 9 mg/kg/d in marmosets). These doses in marmosets represent, respectively, 0.9 and 3.5 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. These doses in rats represent, respectively, 18 and 73 times the maximum recommended dose in humans (MRHD) of valsartan and hydrochlorothiazide based on mg/m^2. (The calculations take an oral dose of 320 mg/day of valsartan in combination with 25 mg/day of hydrochlorothiazide in patients weighing 60 kg).-{}-

The above mentioned effects seem to be caused by the pharmacological effects of the high doses of valsartan (blockage of the angiotensin II-induced inhibition of renin release with the stimulation of the renin producing cells), but these effects have also been found with ACE inhibitors. It seems that these findings lack any relevance in the use of therapeutic doses of valsartan in humans.

The combination of valsartan - hydrochlorothiazide has not been studied regarding mutagenicity, chromosome breakage or carcinogenicity, given that there is no evidence of interaction between the two substances. However, these tests were conducted separately with valsartan and hydrochlorothiazide, and no evidence was found of mutagenicity, chromosome breakage or carcinogenicity.

In rats, toxic maternal doses (600 mg/kg/day) during the last days of gestation and during lactation caused lower survival rates, lower weight increase and delayed development (detachment of the pinna and opening of the ear canal) in offspring (see section 4.6). These doses in rats (600 mg/kg/day) are

approximately 18 times the maximum recommended dose in humans based on mg/m^2 (the calculations assume an oral dose of 320 mg/day and a patient of 60 kg). Similar findings were observed with valsartan/hydrochlorothiazide in rats and in rabbits. In embryo-foetal development (segment II) studies with valsartan/hydrochlorothiazide in rats and rabbits, there was no evidence of teratogenesis; however, foetal toxicity related to maternal toxicity was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose (E-460) + anhydrous colloidal silica.
Sorbitol (E-420i).
Magnesium carbonate (E-504) + pregelatinised maize starch.
Pregelatinised maize starch.
Povidone (E-1201).
Stearyl fumarate and sodium fumarate.
Sodium laurylsulfate.
Crospovidone.
Colloidal anhydrous silica.

Coating:
Lactose monohydrate.
Hypromellose (E-464).
Titanium dioxide (E-171).
Macrogol 4000.
Brown iron oxide (E-172).
Red iron oxide (E-172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

The tablets are packaged in PVC-PE-PVDC (Triplex)/aluminium blisters.

Packages containing 28 (in 7-tablet blister packs) or 280 tablets (in 10-tablet blister packs).
Not all pack sizes may be available for sale.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Laboratorios CINFA, S.A.

C/ Olaz-Chipi, 10 – Polígono Industrial Areta.
31620 Huarte-Pamplona (Navarre) Spain.

8. MARKETING AUTHORISATION NUMBER

Pending

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

November 2010

10. DATE OF REVISION OF THE TEXT