1. NAME OF THE MEDICINAL PRODUCT

Cinfaval 80 mg film-coated tablets
Cinfaval 160 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cinfaval 80 mg film-coated tablets
Each tablet contains 80 mg of valsartan.

Cinfaval 160 mg film-coated tablets
Each tablet contains 160 mg of valsartan.

Excipients:

Cinfaval 80 mg film-coated tablets
contains sorbitol.....9.25 mg
contains lactose.....1.08 mg

Cinfaval 160 mg film-coated tablets
contains sorbitol.....18.50 mg
contains lactose.....2.16 mg

See section 6.1 for the complete list of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Cinfaval 80 mg are scored, pink, cylindrical, coated tablets.
Cinfaval 160 mg are scored, ochre coloured, cylindrical, coated tablets.
The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Treatment of essential hypertension.

Recent myocardial infarction
Treatment of clinically stable patients with symptomatic heart failure or asymptomatic left-ventricular systolic dysfunction after a recent myocardial infarction (12 hours – 10 days) , (see section 4.4 and 5.1).

Heart failure
Treatment of symptomatic heart failure when Angiotensin converting Enzyme (ACE) inhibitors cannot be used or as concomitant treatment with ACE inhibitors when beta-blockers cannot be used (see section 4.4 and 5.1).

4.2 Posology and method of administration

Posology

Hypertension
The recommended starting dose of **Cinfaval** is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are observed after four weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increase to 160 mg If adequately control of blood pressure is not achieved, the daily dose can be increased to 160 mg and to a maximum of 320 mg.
Cinfaval can be administered concomitantly with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide would reduce blood pressure even further in these patients.

Recent myocardial infarction
When patients are clinically stable, the treatment can be initiated 12 hours after the myocardial infarction. After an initial dose of 20 mg twice daily, valsartan should be titrated to 40 mg, 80 mg and 160 mg twice daily during the next few weeks. The initial dose is obtained by splitting the divisible 40 mg tablet.
The target maximum dose is 160 mg twice daily. It is generally recommended that patients reach the 80 mg twice-daily dose two weeks after initiating treatment and the maximum target dose, 160 mg twice daily, after around three months, depending on the patient's tolerability. Reducing the dose of **Cinfaval** should be considered in cases of symptomatic hypotension or altered renal function.
Valsartan may be used concomitantly by patients taking other post-myocardial infarction treatments, e.g. thrombolytics, acetylsalicylic acid, beta blockers, statins and diuretics. Combination with ACE inhibitors is not recommended (see section 4.4 and 5.1).
Evaluation of post-myocardial infarction patients should always include assessment of renal function.

Heart failure
The recommended starting dose of **Cinfaval** is 40 mg twice a day. The dose increments to 80 mg and 160 mg twice daily are to be made at intervals of at least two weeks based on patient tolerance. Reducing the dose of the diuretics taken concomitantly should be considered. The maximum daily dose administered during clinical trials is 320 mg in divided doses.
Valsartan may be administered concomitantly with other treatments for heart failure. However, the triple combination of an ACE inhibitor, a beta blocker and valsartan is not recommended (see section 4.4 and 5.1).
Evaluation of patients with heart failure should always include assessment of renal function.

Method of administration
Cinfaval may be taken independently of a meal and should be administered with water.

Additional information on special populations

Elderly
No dose adjustment is required in elderly patients

Renal impairment
No dosage adjustment is required for patients with a creatinine clearance > 10 ml/min (see sections 4.4 and 5.2).

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

Paediatric patients
Cinfaval is not recommended for use in children under 18 years of age due to the lack of safety and efficacy data.

4.3 Contraindications

- Hypersensitivity to valsartan or to any of its excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Hyperkalemia
The concomitant use of potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium or other agents capable of increasing potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Sodium and/or volume-depleted patients
Patients with severe sodium and/or volume depletion, such as those receiving high doses of diuretics, in rare cases can experience symptomatic hypotension after starting therapy with **Cinfaval**. Therefore, sodium and/or volume depletion should be corrected before commencing treatment with **Cinfaval**; for example, by reducing the diuretic dose.

Renal artery stenosis
The safety of **Cinfaval** has not been established in patients with bilateral renal artery stenosis or stenosis to a solitary kidney.
Short-term administration of **Cinfaval** in 12 patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation
There is no current experience on the safe use of **Cinfaval** in patients who have recently undergone kidney transplant.

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with **Cinfaval** as their renin-angiotensin system is not activated.
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Impaired renal function
No dosage adjustments is required for patients with a creatinine clearance > 10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, valsartan must be used with caution (see sections 4.2 and 5.2).

Recent myocardial infarction
The combination of captopril and valsartan has shown no additional clinical benefit; however, an increase risk of adverse event was seen as compared to treatment with the respective therapies (see section 4.2 and 5.1). Therefore, the combination of valsartan with an ACE inhibitor is not recommended.
Caution is required when starting the treatment in patients after myocardial infarction. Evaluation of post-myocardial infarction patients should always include assessment of renal function (see section 4.2).
The use of **Cinfaval** in patients after myocardial infarction usually causes a blood pressure reduction, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).

Heart failure
In patients with heart failure, the triple combination of an ACE inhibitor, a beta-blocker and valsartan has shown no clinical benefit (see section 5.1). This combination apparently increases the risk of adverse events and is therefore not recommended.
CinfavalCaution should be observed when initiating therapy in patients with heart failure. Evaluation of patients with heart failure should always include assessment of renal function (see section 4.2).
Use of valsartan in patients with heart failure commonly results in some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension is not usually necessary provided dosing instructions are followed (see section 4.2).
In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g. patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and rarely with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of valsartan may be associated with impairment of the renal function.

Pregnancy
Angiotensin II receptor antagonists (AIIRAs) should not be initiated during pregnancy. Unless continue treatment with AIIRAs is considered essential, patients planning to get pregnant should be changed to alternative anti-hypertensive treatments with a known safety profile for use during pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and if appropriate, alternative therapy should be started(see sections 4.3 and 4.6).

Warning about the excipients:
This medicine contains sorbitol. Patients with hereditary intolerance to fructose should not take this medication.
This medicine 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.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with

valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

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

Others
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.**CinfavalCinfaval**

4.6 Pregnancy and lactation

Pregnancy

Use of Angiotensis II Receptor Antagonists (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 sections 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. Whilst there is no controlled epidemiological dataon the risk of administering angiotensin II receptor antagonists (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 should be changed to alternative antihypertensive treatments with a known safety profile for use during pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and if appropriate, an alternative treatment should be started.

Exposure to AIIRAs during the second and third trimester is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia); (see also section 5.3).

If there is AIIRAs exposure from the second trimester of pregnancy, an ultrasound check of renal function and skull is recommended.
Infants whose mothers have been treated with AIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Lactation

Because no information is available regarding the use of this medicinal product during breast-feeding, **Cinfaval** is not recommended and alternative treatments with better establish safety profiles during breast-feeding are preferable, especially while nursing a new-born or preterm infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive 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

In controlled clinical trials in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of adverse reactions did not appear to be related to dose or to the duration of the treatment, and also showed no association with gender, age or race.

The adverse reaction reported in clinical trials, post-marketing experience and laboratory findings are listed below according to system organ class

Adverse reactions are ranked by frequency, the most frequent first, using the following 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), including isolated reports. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

For all the adverse reactions reported from post-marketing experience and laboratory findings, it is not possible to apply any adverse reaction frequency and therefore they are mentioned with a "not known" frequency.

- Hypertension

Blood and lymphatic system disorders

Not known: Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia

Immune system disorders

Not known: Hypersensitivity including serum sickness

Metabolism and nutrition disorders

Not known: Increase of serum potassium

Ear and labyrinth system disorders

Uncommon: Vertigo

Vascular disorders

Not known: Vasculitis

Respiratory, thoracic and mediastinal disorders

Uncommon: Cough

Gastrointestinal disorders

Uncommon: Abdominal pain

Hepato-biliary disorders

Not known Elevation of liver function values including increase of serum bilirubin

Skin and subcutaneous tissue disorders

Not known: Angioedema, rash, pruritus

Musculoskeletal and connective tissue disorders

Not known: Myalgia

Renal and urinary disorders

Not known: Renal failure and impairment, elevation of serum creatinine

General disorders and administration site conditions
Uncommon: Fatigue

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below.

- Post-myocardial infarction and/or heart failure

Blood and lymphatic system disorders
Not known: Thrombocytopenia

Immune system disorders
Not known: Hypersensitivity including serum sickness

Metabolism and nutrition disorders
Uncommon Hyperkalaemia
Not known: Increase of serum potassium

Nervous system disorders
Common: Dizziness, Postural dizziness
Uncommon: Syncope, Headache

Ear and labyrinth system disorders
Uncommon: Vertigo

Cardiac disorders
Uncommon: cardiac failure

Vascular disorders
Common Hypotension, Orthostatic hypotension
Not known: Vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: Cough

Gastrointestinal disorders
Uncommon: Nausea, Diarrhoea

Hepato-biliary disorders
Not known Elevation of liver function values

Skin and subcutaneous tissue disorders
Uncommon Angioedema
Not known: Rash, Pruritus

Musculoskeletal and connective tissue disorders
Not known: Myalgia

Renal and urinary disorders
Common: Renal failure and impairment
Uncommon Acute renal failure, elevation of serum creatinine

Not known: Increase in Blood Urea Nitrogen

General disorders and administration site conditions
Uncommon: Asthenia, Fatigue

4.9 Overdose

Symptoms
An overdose of **Cinfaval** may result in marked hypotension which could lead to depressed level of conciousness, circulatory collapse and/or shock.

Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition is of prime importance.
If hypotension occurs, the patient should be placed in a supine position and blood volume correction should be undertaken.
Valsartan is unlikely to be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists, plain, ATC code: C09C A03.
Valsartan is an orally active, potent, 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 is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. 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 ($P<0.05$).**Cinfaval**

<u>Hypertension</u>
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 antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a significant additional reduction in blood pressure is achieved.
Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced ($p<0.001$) by 42% (–24.2 µg/min; 95% CI: –40.4 to –19.1) with valsartan and approximately 3% (–1.7 µg/min; 95% CI: –5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.
The valsartan Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE 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). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95%CI: 22 to 47%), and by 44% with valsartan 320 mg (95%CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.**Cinfaval**

Recent myocardial infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomised, controlled, multinational double blind study conducted in 14,703 patients with acute myocardial infarction and signs, symptoms or radiological evidence of congestive heart failure and/or evidence of left ventricle systolic dysfunction (manifested as an ejection fraction ≤40 % by radionuclide ventriculography, or ≤35 % by echocardiography or ventricular contrast angiography). The patients were randomised between 12 hours to 10 days after the onset of the symptoms of myocardial infarction to valsartan, captopril or the combination of both. The mean duration of treatment was two years.
Valsartan was as effective as captopril in reducing all-cause mortality from any cause after myocardial infarction. All-cause mortality was similar in the groups on valsartan (19.9 %), captopril (19.5 %) and valsartan + captopril (19.3 %) groups. The combination of valsartan and captopril had no additional benefit over captopril alone. No differences were observed between valsartan and captopril in all-cause mortality based on age, gender, race, baseline therapies or underlying disease. Valsartan was also effective in prolonging time to and reducing cardiovascular mortality, hospitalisation due to heart failure, recurrent myocardial infarction, resuscitated cardiac arrest, and non-fatal stroke (secondary composite endpoint).
The safety profile of valsartan was consistent with the clinical course of patients treated in the post-myocardial infarction setting. Regarding renal function, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients, 4.8% of valsartan+captopril-treated patients, and 3.4% of captopril-treated patients. Discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients, 1.3% in valsartan+captopril patients, and 0.8% of captopril patients. An assessment of renal function should be included in the evaluation of patients post-myocardial infarction.
No differences were observed in al-cause mortality cardiovascular mortality or morbidity when beta-blockers were administered together with the combination of valsartan + captopril, valsartan alone or captopril alone. Irrespective of treatment, mortality was lower in the patient group treated with a beta-blocker, suggesting that the known benefit of the beta-blocker in this population was maintained in this trial.

Heart failure

Val-HeFT was a randomised, controlled, multinational clinical trial of valsartan compared with placebo on morbidity and mortality in 5,010 NYHA class II (62 %), III (36 %) and IV (2 %) heart failure patients receiving usual therapy with LVEF lower than 40 % and internal left ventricle diastolic diameter (ILVDD) greater than 2.9 cm/cm2. The underlying treatment

included ACE inhibitors (93 %), diuretics (86 %), digoxin (67 %) and beta-blockers (36 %). The mean duration of the follow-up was nearly two years. The mean daily dose of valsartan in Val-HeFT was 254 mg.
The study had 2 primary endpoints: all-cause mortality (time to death) and composite mortality and heart failure morbidity (time to first morbid event) defined as death, sudden death with resuscitation, hospitalisation for heart failure or administration of intravenous inotropic or vasodilator agents for at least four hours without hospitalisation.
All-cause mortality was similar (p=NS) in the valsartan (19.7%) and placebo (19.4%) groups. The primary benefit was a reduction of the risk of 27.5 % (95% CI: 17 to 37%) reduction in risk for the time to heart failure hospitalisation (13.9 % vs 18.5 %).
Results appearing to favour placebo (composite mortality and morbidity was 21.9% in placebo vs. 25.4% in valsartan group) were observed for those patients receiving the triple combination of an ACE inhibitor, a beta blocker and valsartan.
In a subgroup of patients not receiving an ACE inhibitor (n=366), the morbidity benefits were greatest. In this subgroup all-cause mortality was significantly reduced with valsartan compared to placebo by 33% (95% CI: –6% to 58%) (17.3% valsartan vs. 27.1% placebo) and the composite mortality and morbidity risk was significantly reduced by 44% (24.9% valsartan vs. 42.5% placebo).
In patients receiving an ACE inhibitor without a beta-blocker, all-cause mortality was similar (p=NS) in the valsartan (21.8%) and placebo (22.5%) groups. Composite mortality and morbidity risk was significantly reduced by 18.3% (95% CI: 8% to 28%) with valsartan compared with placebo (31.0% vs. 36.3%).
In the overall Val-HeFT population, valsartan treated patients showed significant improvement in NYHA class, and heart failure signs and symptoms, including dyspnoea, fatigue, oedema and rales compared to placebo. Patients treated with valsartan had a better quality of life as demonstrated by change in the Minnesota Living with Heart Failure Quality of Life score from baseline at endpoint than placebo. Ejection fraction in valsartan treated patients was significantly increased and LVIDD significantly reduced from baseline at endpoint compared to placebo.

5.2 Pharmacokinetic properties

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

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

Biotransformation:
Valsartan is not bio transformed 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.

Excretion:
Valsartan shows multiexponential decay kinetics ($t_{½\alpha}$ <1 h and $t_{½\beta}$ about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in 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. **Cinfaval**

In Heart failure patients:
The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and Cmax values of valsartan are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 l/h. Age does not affect the apparent clearance in heart failure patients.

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 be clinically significant.

Impaired renal function
As expected from where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Therefore, no dose adjustment is required in patients with renal impairment (creatinine clearance > 10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4).

Hepatic Impairment
Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. valsartan has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 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 non-clinical safety studies, high doses of valsartan in rats (200 to 600 mg/kg body weight) caused a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (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/m^2 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 observed in both species. It was considered that these changes were caused by the pharmacological action of valsartan which causes prolonged hypotension, particularly in marmosets. At therapeutic doses of valsartan in humans, hypertrophy of the renal juxtaglomerular renal cells does not appear to be relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: microcrystalline cellulose (E-460), colloidal anhydrous silica, sorbitol (E-420), magnesium carbonate (E-504), pregelatinised starch, povidone (E-1201), sodium stearyl fumarate, sodium lauryl sulphate and crospovidone.

Coating: Opadry OY-L-28900 (lactose monohydrate, hypromellose (E-464), titanium dioxide (E-171), macrogol).

Cinfaval 80 mg contains red iron oxide (E-172).
Cinfaval 160 mg contains yellow/brown iron oxide (E-172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a temperature less than 30ºC.

6.5 Nature and contents of container

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

Cinfaval 80 mg is supplied in packages containing 28 tablets.
Cinfaval 160 mg is supplied in packages containing 28 tablets.

6.6 Special precautions for disposal

The disposal of the unused drug and all materials in contact with it will be performed according to the local regulations.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS CINFA, S.A.
Olaz-Chipi, 10 – Polígono Areta
31620 Huarte-Pamplona (Navarra)

8. MARKETING AUTHORISATION NUMBER(S)

Cinfaval**Cinfaval**Pending

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT