Public Assessment Report

Decentralised Procedure

Valsartan and Hydrochlorothiazide
80mg/12.5mg, 160mg/12.5mg, 160mg 25mg,
320mg/12.5 and 320mg/25mg Film-Coated Tablets

Valsartan
Hydrochlorothiazide

UK/H/3712/001-5/DC

UK licence no: PL 20658/0037-40 and 48

Torrent Pharma GmbH
On 6th April 2011, the Reference Member State (RMS) and the Concerned Member States (CMSs) agreed to grant Marketing Authorisations to Torrent Pharma GmbH for the medicinal products Valsartan and Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5 and 320mg/25mg Film-Coated Tablets. After the national phase, a licence was granted in the UK on 6th May 2011. These medicines are only available on prescription from your doctor.

Valsartan and Hydrochlorothiazide Film-Coated Tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension).

- Valsartan belongs to a class of medicines known as “angiotensin II receptor antagonists”, which help to control high blood pressure. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing your blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.

- Hydrochlorothiazide belongs to a group of medicines called thiazide diuretics (also known as “water tablets”). Hydrochlorothiazide increases urine output, which also lowers blood pressure.

Valsartan and Hydrochlorothiazide Film-Coated Tablets are used to treat high blood pressure which is not adequately controlled either by valsartan or hydrochlorothiazide alone.

High blood pressure increases the workload of the heart and arteries. If not treated, it can damage the blood vessels of the brain, heart and kidneys, and may result in a stroke, heart failure or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Valsartan and Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5 and 320mg/25mg Film-Coated Tablets outweigh the risks, hence Marketing Authorisations have been granted.
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Module 6 Steps taken after initial procedure
# Module 1

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<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1 and hybrid, 10.3</td>
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<td><strong>Active Substance</strong></td>
<td>valsartan and hydrochlorothiazide</td>
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<td><strong>Form</strong></td>
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<td><strong>Strength</strong></td>
<td>80 mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg Film-Coated Tablets</td>
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</tbody>
</table>
| **MA Holder** | Torrent Pharma GmbH  
Suedwestpark 50  
90449 Nuremberg  
Germany                                                                                                      |
| **RMS** | UK                                                                                                                                 |
| **CMS** | Germany, Italy, Lithuania and Romania                                                                                                       |
| **Procedure Numbers** | UK/H/3712/001-5/DC                                                                                                                         |
| **Timetable** | Day 210 – 6th April 2011                                                                                                                  |
Module 2
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Valsartan and Hydrochlorothiazide 80 mg/12.5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.
One tablet contains 174.45 mg lactose as lactose-monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Valsartan and Hydrochlorothiazide 80 mg/12.5 mg Film-Coated Tablets are white to off white, oval shaped, bevelled edge, biconvex film coated tablets debossed with “1071” on one side and plain on the other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Valsartan and Hydrochlorothiazide Film-Coated Tablets fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
Posology
The recommended dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 80 mg/12.5 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.
The clinical response to Valsartan and Hydrochlorothiazide Film-Coated Tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/25 mg.
The antihypertensive effect is substantially present within 2 weeks.
In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.
If no relevant additional effect is seen with Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

Method of administration
Valsartan and Hydrochlorothiazide Film-Coated Tablets can be taken with or without food and should be administered with water.

Special populations
Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mls/min). Due to the hydrochlorothiazide component, Valsartan and Hydrochlorothiazide Film-Coated Tablets are 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 dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan and Hydrochlorothiazide Film-Coated Tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).
Elderly
No dose adjustment is required in elderly patients.

Paediatric patients
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
Second and third trimester of pregnancy (section 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, and symptomatic hyperuricaemia.
Dialysis.

4.4 Special warnings and precautions for use

Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended.
Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraeemic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan and Hydrochlorothiazide Film-Coated Tablets. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan and Hydrochlorothiazide Film-Coated Tablets as well may be associated with impairment of the renal function. Valsartan and Hydrochlorothiazide Film-Coated Tablets should not be used in these patients.

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

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

Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 ml/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan and Hydrochlorothiazide Film-Coated Tablets are used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan and Hydrochlorothiazide Film-Coated Tablets should be used with caution (see sections 4.2 and 5.2).

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

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in 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).

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test. This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended

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

Concomitant use requiring caution

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

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

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan and Hydrochlorothiazide Film-Coated Tablets and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan

Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan and Hydrochlorothiazide Film-Coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of plasma levels of potassium is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiame, amisulpride, tiapride, pimozide, haloperidol, droperidol)
Others (e.g. bepridil, cisapride, diphemanil, erythromycin i. v., halofantrin, ketanserin, mizolastin, pentamidine, sparflxacine, terfenadine, vincamine i. v.)
Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.6 Pregnancy and lactation

#### Pregnancy

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise fetal-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

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

Fertility
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

4.7 Effects on ability to drive and use machines
No studies on the effect of Valsartan and Hydrochlorothiazide Film-Coated Tablets, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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

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

Table 1: Frequency of adverse reactions with valsartan/hydrochlorothiazide

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
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<tbody>
<tr>
<td>Uncommon</td>
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<tr>
<td>Dehydration</td>
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</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
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</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>
Syncope

**Eye disorders**
Uncommon
Vision blurred

**Ear and labyrinth disorders**
Uncommon
Tinnitus

**Vascular disorders**
Uncommon
Hypotension

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

**Gastrointestinal disorders**
Very rare
Diarrhoea

**Musculoskeletal and connective tissue disorders**
Uncommon
Myalgia
Very rare
Arthralgia

**Renal and urinary disorders**
Not known
Impaired renal function

**General disorders and administration site conditions**
Uncommon
Fatigue

**Investigations**
Not known
Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

**Additional information on the individual components**
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan and Hydrochlorothiazide Film-Coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

**Table 2: Frequency of adverse reactions with Valsartan**

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

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

**Metabolism and nutrition disorders**
Not known
Increase of serum potassium

**Ear and labyrinth disorders**
Uncommon
Vertigo

**Vascular disorders**
Not known
Vasculitis

**Gastrointestinal disorders**
Uncommon
Abdominal pain

**Hepatobiliary disorders**
Not known
Elevation of liver function values
Skin and subcutaneous tissue disorders
Not known
Angioedema, rash, pruritus

Renal and urinary disorders
Not known
Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan and Hydrochlorothiazide Film-Coated Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

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

Immune system disorders
Very rare
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
Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Reproductive system and breast disorders
Common
Impotence
4.9 Overdose

Symptoms

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

Treatment

The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.

If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.

Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics.

ATC code: C09DA03.

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on hydrochlorothiazide 12.5 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (14.9/11.3 mmHg) compared to hydrochlorothiazide 12.5 mg (5.2/2.9 mmHg) and hydrochlorothiazide 25 mg (6.8/5.7 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (60%) compared to hydrochlorothiazide 12.5 mg (25%) and hydrochlorothiazide 25 mg (27%).

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 80 mg, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (9.8/8.2 mmHg) compared to valsartan 80 mg (3.9/5.1 mmHg) and valsartan 160 mg (6.5/6.2 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (51%) compared to valsartan 80 mg (36%) and valsartan 160 mg (37%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 80/12.5 mg (16.5/11.8 mmHg) compared to placebo (1.9/4.1 mmHg) and both hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg) and valsartan 80 mg (8.8/8.6 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 80/12.5 mg (64%) compared to placebo (29%) and hydrochlorothiazide (41%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

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.

Valsartan

Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

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does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan 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) lower 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).

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 2–4 weeks and is sustained 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 Diovan 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 randomised 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.

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

5.2 Pharmacokinetic properties

**Valsartan/hydrochlorothiazide**

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan 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 active substance given alone, or placebo.
Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (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 biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multiexponential decay kinetics (t½α <1 h and t½β about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide

Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (tmax about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. 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.

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

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

Special populations
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; 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 Valsartan and Hydrochlorothiazide Film-Coated Tablets no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min. In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan and Hydrochlorothiazide Film-Coated Tablets. 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 was increased approximately 2-fold compared with healthy volunteers.
There is no data available on the use of valsartan in patients with severe hepatic dysfunction (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/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)
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). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient). 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 arterioles (at 600 + 188 mg/kg/day in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).
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.
In rats, maternally toxic doses of valsartan (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). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

Paediatric population
Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan
study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Croscarmellose sodium
Povidone
Magnesium stearate
Talc

Film-coat:
Hyromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Valsartan and Hydrochlorothiazide 80 mg/12.5 mg Film-Coated Tablets are available in Al/OPA-Al-PVC blister packs with 28 tablets.

6.6 Special precautions for disposal
No special requirements.
1 **NAME OF THE MEDICINAL PRODUCT**
Valsartan and Hydrochlorothiazide 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.
One tablet contains 325.3 mg lactose as lactose-monohydrate.
For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**
Film-coated tablet
Valsartan and Hydrochlorothiazide 160 mg/12.5 mg Film-Coated Tablets are pink coloured, oval shaped, bevelled edge, biconvex film coated tablets debossed with “1072” on one side and plain on other side.

4 **CLINICAL PARTICULARS**
4.1 **Therapeutic indications**
Treatment of essential hypertension in adults.
Valsartan and Hydrochlorothiazide Film-Coated Tablets fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 **Posology and method of administration**
**Posology**
The recommended dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 160 mg/12.5 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.
The clinical response to Valsartan and Hydrochlorothiazide Film-Coated Tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/25 mg.
The antihypertensive effect is substantially present within 2 weeks.
In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.
If no relevant additional effect is seen with Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

**Method of administration**
Valsartan and Hydrochlorothiazide Film-Coated Tablets can be taken with or without food and should be administered with water.

**Special populations**
**Renal impairment**
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mls/min). Due to the hydrochlorothiazide component, Valsartan and Hydrochlorothiazide Film-Coated Tablets are 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 dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan and Hydrochlorothiazide Film-Coated Tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

**Elderly**
No dose adjustment is required in elderly patients.
Paediatric patients
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
Second and third trimester of pregnancy (section 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, and symptomatic hyperuricaemia Dialysis.

4.4 Special warnings and precautions for use
Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.
Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraeamic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia. As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan and Hydrochlorothiazide Film-Coated Tablets. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan and Hydrochlorothiazide Film-Coated Tablets as well may be associated with impairment of the renal function. Valsartan and Hydrochlorothiazide Film-Coated Tablets should not be used in these patients.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan and Hydrochlorothiazide Film-Coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 mls/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan and Hydrochlorothiazide Film-Coated Tablets are used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan and Hydrochlorothiazide Film-Coated Tablets should be used with caution (see sections 4.2 and 5.2).

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

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.
Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in 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).

General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.
Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interaction with other medicinal products and other forms of interaction

4.5.1.1 Concomitant use not recommended

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

Concomitant use requiring caution
Other antihypertensive agents
Valsartan and Hydrochlorothiazide Film-Coated Tablets may increase the effects of other agents with antihypertensive properties (e.g. ACEI, beta-blockers, calcium channel blockers).

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

*Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs*
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan and Hydrochlorothiazide Film-Coated Tablets and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

### Interactions related to valsartan

**Concomitant use not recommended**

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

**No interaction**
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan and Hydrochlorothiazide Film-Coated Tablets (see interactions related to hydrochlorothiazide).

### Interactions related to hydrochlorothiazide

**Concomitant use requiring caution**

Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of plasma levels of potassium is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulprolide, amisulpride, tiapride, pimozide, haloperidol, droperidol)
Others (e.g. bepridil, cisapride, diphenamid, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine i.v.)
Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

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

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

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

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

**Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)**

Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

**Anticholinergic agents (e.g. atropine, biperiden)**

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

**Amantadine**

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

**Cholestyramine and cholestipol resins**

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

**Cytotoxic agents (e.g. cyclophosphamide, methotrexate)**

Thiazides, including hydrochlorothiazide, may reduce renal excretion of cytotoxic agents and potentiate their myelosuppressive effects.

**Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine)**

Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.

**Ciclosporin**

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

**Alcohol, anaesthetics and sedatives**

Potentiation of orthostatic hypotension may occur.

**Methyldopa**

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

**Carbamazepine**

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

**Iodine contrast media**

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

### 4.6 Pregnancy and lactation

**Pregnancy**

**Valsartan**

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-
hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

**Hydrochlorothiazide**

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

**Lactation**

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

**Fertility**

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

### 4.7 Effects on ability to drive and use machines

No studies on the effect of Valsartan and Hydrochlorothiazide Film-Coated Tablets, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

### 4.8 Undesirable effects

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

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

#### Table 1: Frequency of adverse reactions with valsartan/hydrochlorothiazide

**Metabolism and nutrition disorders**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Dehydration</td>
<td></td>
</tr>
</tbody>
</table>

**Nervous system disorders**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Paraesthesia</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
</tr>
</tbody>
</table>

**Eye disorders**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Vision blurred</td>
<td></td>
</tr>
</tbody>
</table>

**Ear and labyrinth disorders**


Uncommon
Tinnitus
**Vascular disorders**
Uncommon
Hypotension
**Respiratory, thoracic and mediastinal disorders**
Uncommon
Cough
Not known
Non cardiogenic pulmonary oedema
**Gastrointestinal disorders**
Very rare
Diarrhoea
**Musculoskeletal and connective tissue disorders**
Uncommon
Myalgia
Very rare
Arthralgia
**Renal and urinary disorders**
Not known
Impaired renal function
**General disorders and administration site conditions**
Uncommon
Fatigue
**Investigations**
Not known
Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

**Additional information on the individual components**
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan and Hydrochlorothiazide Film-Coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

**Table 2: Frequency of adverse reactions with Valsartan**

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

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

**Metabolism and nutrition disorders**
Not known
Increase of serum potassium

**Ear and labyrinth disorders**
Uncommon
Vertigo

**Vascular disorders**
Not known
Vasculitis

**Gastrointestinal disorders**
Uncommon
Abdominal pain

**Hepatobiliary disorders**
Not known
Elevation of liver function values

**Skin and subcutaneous tissue disorders**
Not known
Angioedema, rash, pruritus

**Renal and urinary disorders**
Not known
Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan and Hydrochlorothiazide Film-Coated Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

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

**Immune system disorders**
- Very rare
- 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
- Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

**Reproductive system and breast disorders**
- Common
- Impotence

4.9 Overdose

**Symptoms**
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance. If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly. Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics.
ATC code: C09D A03.

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

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%), and valsartan 160 mg (59%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

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.

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

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 2–4 weeks and is sustained 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 Diovan 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 randomised 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.

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

5.2 Pharmacokinetic properties
Valsartan/hydrochlorothiazide
The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan 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 active substance given alone, or placebo.
Valsartan

Absorption
Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (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 biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multiexponential decay kinetics (t½α <1 h and t½β about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide

Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (tmax about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. 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.

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

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

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; 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 Valsartan and Hydrochlorothiazide Film-Coated Tablets no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min.
In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan and Hydrochlorothiazide Film-Coated Tablets. 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 was increased approximately 2-fold compared with healthy volunteers.
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/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

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). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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 arterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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.

In rats, maternally toxic doses of valsartan (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). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

**Paediatric population**

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
- Lactose monohydrate
- Croscarmellose sodium
- Povidone
- Magnesium stearate
- Talc

Film-coat:
- Hypromellose
- Titanium dioxide (E171)
- Macrogol 400
- Ferric oxide red (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Valsartan and Hydrochlorothiazide 160 mg/12.5 mg Film-Coated Tablets are available in Al/OPA-Al-PVC blister packs with 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20658/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/05/2011

10 DATE OF REVISION OF THE TEXT

06/05/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan and Hydrochlorothiazide 160 mg/25 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.
One tablet contains 348.9 mg lactose as lactose-monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Valsartan and Hydrochlorothiazide 160 mg/25 mg Film-Coated Tablets are yellow coloured, oval shaped, bevelled edge, biconvex film coated tablets with a score line on both the side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Valsartan and Hydrochlorothiazide Film-Coated Tablets fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration

Posology
The recommended dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 160 mg/25 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.

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

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

The antihypertensive effect is substantially present within 2 weeks. In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.

If no relevant additional effect is seen with Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

Method of administration
Valsartan and Hydrochlorothiazide Film-Coated Tablets can be taken with or without food and should be administered with water.

Special populations
Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mls/min). Due to the hydrochlorothiazide component, Valsartan and Hydrochlorothiazide Film-Coated Tablets are 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 dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan and Hydrochlorothiazide Film-Coated Tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
No dose adjustment is required in elderly patients.
Paediatric patients
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
Second and third trimester of pregnancy (section 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, and symptomatic hyperuricaemia.
Dialysis.

4.4 Special warnings and precautions for use
Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloraeamic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan and Hydrochlorothiazide Film-Coated Tablets. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan and Hydrochlorothiazide Film-Coated Tablets as well may be associated with impairment of the renal function. Valsartan and Hydrochlorothiazide Film-Coated Tablets should not be used in these patients.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan and Hydrochlorothiazide Film-Coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance $\geq 30$ mls/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan and Hydrochlorothiazide Film-Coated Tablets are used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan and Hydrochlorothiazide Film-Coated Tablets should be used with caution (see sections 4.2 and 5.2).

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

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in 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).

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended

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

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

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

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan and Hydrochlorothiazide Film-Coated Tablets and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan and Hydrochlorothiazide Film-Coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbamazepine, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of plasma levels of potassium is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiame, amisulpride, tiapride, pimozide, haloperidol, droperidol)
Others (e.g. bepridil, cisapride, diphenhydramine, erythromycin i.v., halofantrine, ketanserin, mizolastine, pentamidine, sparflaxacine, terfenadine, vincaline i.v.)
Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.6 Pregnancy and lactation

#### Pregnancy

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot
be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

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

Fertility
Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

4.7 Effects on ability to drive and use machines
No studies on the effect of Valsartan and Hydrochlorothiazide Film-Coated Tablets, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

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

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

Table 1: Frequency of adverse reactions with valsartan/hydrochlorothiazide

Metabolism and nutrition disorders
Uncommon
Dehydration

Nervous system disorders
Very rare
Dizziness
Uncommon
Paraesthesia
Not known
Syncope

Eye disorders
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-Coated Tablets

Uncommon
Vision blurred

**Ear and labyrinth disorders**
Uncommon
Tinnitus

**Vascular disorders**
Uncommon
Hypotension

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

**Gastrointestinal disorders**
Very rare
Diarrhoea

**Musculoskeletal and connective tissue disorders**
Uncommon
Myalgia
Very rare
Arthralgia

**Renal and urinary disorders**
Not known
Impaired renal function

**General disorders and administration site conditions**
Uncommon
Fatigue

**Investigations**
Not known
Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

**Additional information on the individual components**
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan and Hydrochlorothiazide Film-Coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

**Table 2: Frequency of adverse reactions with Valsartan**

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

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

**Metabolism and nutrition disorders**
Not known
Increase of serum potassium

**Ear and labyrinth disorders**
Uncommon
Vertigo

**Vascular disorders**
Not known
Vasculitis

**Gastrointestinal disorders**
Uncommon
Abdominal pain

**Hepatobiliary disorders**
Not known
Elevation of liver function values

**Skin and subcutaneous tissue disorders**
Not known
Angioedema, rash, pruritus

Renal and urinary disorders
Not known
Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide

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

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

**Immune system disorders**
Very rare
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
Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

**Reproductive system and breast disorders**
Common
Impotence

4.9 Overdose

**Symptoms**

Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.
If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics.
ATC code: C09DA03.

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

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 160 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 160/25 mg (14.6/11.9 mmHg) and valsartan/hydrochlorothiazide 160/12.5 mg (12.4/10.4 mmHg) compared to valsartan 160 mg (8.7/8.8 mmHg). The difference in BP reductions between the 160/25 mg and 160/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (68%) and 160/12.5 mg (62%) compared to valsartan 160 mg (49%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 160/12.5 mg (17.8/13.5 mmHg) and 160/25 mg (22.5/15.3 mmHg) compared to placebo (1.9/4.1 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (7.3/7.2 mmHg), hydrochlorothiazide 25 mg (12.7/9.3 mmHg) and valsartan 160 mg (12.1/9.4 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 160/25 mg (81%) and valsartan/hydrochlorothiazide 160/12.5 mg (76%) compared to placebo (29%) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (41%), hydrochlorothiazide 25 mg (54%), and valsartan 160 mg (59%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

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.

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

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 2–4 weeks and is sustained 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 Diovan 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 randomised 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.

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

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan 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 active substance given alone, or placebo.
Valsartan
Absorption
Following oral administration of valsartan alone, peak plasma concentrations 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 biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Elimination
Valsartan shows multiexponential decay kinetics (t½α<1 h and t½ß about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Hydrochlorothiazide
Absorption
The absorption of hydrochlorothiazide, after an oral dose, is rapid (tmax about 2 h), with similar absorption characteristics for both suspension and tablet formulations. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. 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.

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

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

Special populations
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; 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 Valsartan and Hydrochlorothiazide Film-Coated Tablets no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min. In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan and Hydrochlorothiazide Film-Coated Tablets. 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 was increased approximately 2-fold compared with healthy volunteers.
There is no data available on the use of valsartan in patients with severe hepatic dysfunction (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/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

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). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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 arterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m2 basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

In rats, maternally toxic doses of valsartan (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). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

Paediatric population

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Core:
Lactose monohydrate
Crocarmellose sodium
Povidone
Magnesium stearate
Talc

Film-coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Ferric oxide yellow (E 172)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Valsartan and Hydrochlorothiazide 160 mg/25 mg Film-Coated Tablets are available in Al/OPA-Al-PVC blister packs with 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
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E-Mail: mail@torrentpharma.de

8 MARKETING AUTHORISATION NUMBER(S)
PL 20658/0039

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/05/2011

10 DATE OF REVISION OF THE TEXT
06/05/2011
NAME OF THE MEDICINAL PRODUCT
Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 320 mg of valsartan and 25 mg of hydrochlorothiazide.
One tablet contains 650.6 mg lactose as lactose-monohydrate.
For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Film-coated tablet
Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets are white to off white, oval shaped, bevelled edge, biconvex film coated tablets with score line on one side and plain on other side. The tablet can be divided into equal halves.

CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Valsartan and Hydrochlorothiazide Film-Coated Tablets fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
Posology
The recommended dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/25 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.
The clinical response to Valsartan and Hydrochlorothiazide Film-Coated Tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/25 mg.
The antihypertensive effect is substantially present within 2 weeks. In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.
If no relevant additional effect is seen with Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

Method of administration
Valsartan and Hydrochlorothiazide Film-Coated Tablets can be taken with or without food and should be administered with water.

Special populations
Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mls/min). Due to the hydrochlorothiazide component, Valsartan and Hydrochlorothiazide Film-Coated Tablets are 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 dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan and Hydrochlorothiazide Film-Coated Tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Elderly
No dose adjustment is required in elderly patients.
Paediatric patients
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
Second and third trimester of pregnancy (section 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, and symptomatic hyperuricaemia.
Dialysis.

4.4 Special warnings and precautions for use
Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.
Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloremic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan and Hydrochlorothiazide Film-Coated Tablets. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan and Hydrochlorothiazide Film-Coated Tablets as well may be associated with impairment of the renal function. Valsartan and Hydrochlorothiazide Film-Coated Tablets should not be used in these patients.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan and Hydrochlorothiazide Film-Coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance \( \geq 30 \) mls/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan and Hydrochlorothiazide Film-Coated Tablets are used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan and Hydrochlorothiazide Film-Coated Tablets should be used with caution (see sections 4.2 and 5.2).

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

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in 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).

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

Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test. This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended

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

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

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

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan and Hydrochlorothiazide Film-Coated Tablets and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan and Hydrochlorothiazide Film-Coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of plasma levels of potassium is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiame, amisulpride, tiapride, pimozide, haloperidol, droperidol)
Others (e.g. bepridil, cisapride, diphenidol, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine i.v.)
Due to the risk of hypokalemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.6 Pregnancy and lactation

#### Pregnancy

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot
be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Lactation

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

Fertility

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

4.7 Effects on ability to drive and use machines

No studies on the effect of Valsartan and Hydrochlorothiazide Film-Coated Tablets, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

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

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

Table 1: Frequency of adverse reactions with valsartan/hydrochlorothiazide

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Dehydration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Parasthesia</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
</tr>
</thead>
</table>
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

Uncommon
Vision blurred

**Ear and labyrinth disorders**
Uncommon
Tinnitus

**Vascular disorders**
Uncommon
Hypotension

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

**Gastrointestinal disorders**
Very rare
Diarrhoea

**Musculoskeletal and connective tissue disorders**
Uncommon
Myalgia
Very rare
Arthralgia

**Renal and urinary disorders**
Not known
Impaired renal function

**General disorders and administration site conditions**
Uncommon
Fatigue

**Investigations**
Not known
Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

**Additional information on the individual components**
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan and Hydrochlorothiazide Film-Coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

**Table 2: Frequency of adverse reactions with Valsartan**

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

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

**Metabolism and nutrition disorders**
Not known
Increase of serum potassium

**Ear and labyrinth disorders**
Uncommon
Vertigo

**Vascular disorders**
Not known
Vasculitis

**Gastrointestinal disorders**
Uncommon
Abdominal pain

**Hepatobiliary disorders**
Not known
Elevation of liver function values

**Skin and subcutaneous tissue disorders**
Not known
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-Coated Tablets

Angioedema, rash, pruritus

**Renal and urinary disorders**
Not known
Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide
Hydrochlorothiazide has been extensively prescribed for many years, frequently in higher doses than those administered with Valsartan and Hydrochlorothiazide Film-Coated Tablets. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

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

**Immune system disorders**
Very rare
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
Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

**Reproductive system and breast disorders**
Common
Impotence

4.9 **Overdose**

**Symptoms**
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance.
If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly.
Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics.
ATC code: C09D A03.

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 320 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 320/25 mg (15.4/10.4 mmHg) and valsartan/hydrochlorothiazide 320/12.5 mg (13.6/9.7 mmHg) compared to valsartan 320 mg (6.1/5.8 mmHg).
The difference in systolic BP reduction between the 320/25 mg and 320/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (75%) and 320/12.5 mg (69%) compared to valsartan 320 mg (53%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 320/12.5 mg (21.7/15.0 mmHg) and 320/25 mg (24.7/16.6 mmHg) compared to placebo (7.0/5.9 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (11.1/9.0 mmHg), hydrochlorothiazide 25 mg (14.5/10.8 mmHg) and valsartan 320 mg (13.7/11.3 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (85%) and 320/12.5 mg (83%) compared to placebo (45%) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (60%), hydrochlorothiazide 25 mg (66%), and valsartan 320 mg (69%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

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.

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

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 2–4 weeks and is sustained 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 Diovan 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 randomised 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.

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

5.2 Pharmacokinetic properties

Valsartan/hydrochlorothiazide

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan 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 active substance given alone, or placebo.

Valsartan

Absorption

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (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.
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

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

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

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

Hydrochlorothiazide
Absorption
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. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. 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.

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

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

Special populations
Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; 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 Valsartan and Hydrochlorothiazide Film-Coated Tablets no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min.

In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan and Hydrochlorothiazide Film-Coated Tablets. 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 was increased approximately 2-fold compared with healthy volunteers.

There is no data available on the use of valsartan in patients with severe hepatic dysfunction (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/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

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). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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 arterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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.

In rats, maternally toxic doses of valsartan (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). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

Paediatric population

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.
6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Valsartan and Hydrochlorothiazide 320 mg/12.5 mg Film-Coated Tablets are available in Al/OPA-Al-PVC blister packs with 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
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8 MARKETING AUTHORISATION NUMBER(S)
PL 20658/0040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/05/2011

10 DATE OF REVISION OF THE TEXT
06/05/2011
1 NAME OF THE MEDICINAL PRODUCT
Valsartan and Hydrochlorothiazide 320 mg/12.5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 320 mg of valsartan and 12.5 mg of hydrochlorothiazide.
One tablet contains 627.3 mg lactose as lactose-monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet
Valsartan and Hydrochlorothiazide 320 mg/12.5 mg Film-Coated Tablets are pink coloured, oval shaped, bevelled edge biconvex film coated tablets debossed with “1074” on one side and plain on other side.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of essential hypertension in adults.
Valsartan and Hydrochlorothiazide Film-Coated Tablets fixed-dose combination is indicated in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy.

4.2 Posology and method of administration
Posology
The recommended dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/12.5 mg is one film-coated tablet once daily. Dose titration with the individual components is recommended. In each case, up-titration of individual components to the next dose should be followed in order to reduce the risk of hypotension and other adverse events.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled on valsartan or hydrochlorothiazide monotherapy, provided the recommended dose titration sequence for the individual components is followed.
The clinical response to Valsartan and Hydrochlorothiazide Film-Coated Tablets should be evaluated after initiating therapy and if blood pressure remains uncontrolled, the dose may be increased by increasing either one of the components to a maximum dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets 320 mg/25 mg.
The antihypertensive effect is substantially present within 2 weeks.
In most patients, maximal effects are observed within 4 weeks. However, in some patients, 4-8 weeks treatment may be required. This should be taken into account during dose-titration.
If no relevant additional effect is seen with Valsartan and Hydrochlorothiazide 320 mg/25 mg Film-Coated Tablets after 8 weeks, treatment with an additional or alternative antihypertensive medicinal product should be considered (see section 5.1).

Method of administration
Valsartan and Hydrochlorothiazide Film-Coated Tablets can be taken with or without food and should be administered with water.

Special populations
Renal impairment
No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance ≥30 mls/min). Due to the hydrochlorothiazide component, Valsartan and Hydrochlorothiazide Film-Coated Tablets are 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 dose of valsartan should not exceed 80 mg (see section 4.4). Valsartan and Hydrochlorothiazide Film-Coated Tablets are contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).
Elderly
No dose adjustment is required in elderly patients.
Paediatric patients
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications
Hypersensitivity to valsartan, hydrochlorothiazide, other sulfonamide-derived medicinal products or to any of the excipients.
Second and third trimester of pregnancy (section 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, and symptomatic hyperuricaemia.
Dialysis.

4.4 Special warnings and precautions for use
Serum electrolyte changes
Valsartan
Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended.
Monitoring of potassium should be undertaken as appropriate.
Hydrochlorothiazide
Hypokalaemia has been reported under treatment with thiazide diuretics, including hydrochlorothiazide. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, including hydrochlorothiazide, has been associated with hyponatraemia and hypochloremic alkalosis. Thiazides, including hydrochlorothiazide, increase the urinary excretion of magnesium, which may result in hypomagnesaemia. Calcium excretion is decreased by thiazide diuretics. This may result in hypercalcaemia.
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Sodium and/or volume-depleted patients
Patients receiving thiazide diuretics, including hydrochlorothiazide, should be observed for clinical signs of fluid or electrolyte imbalance.
In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Valsartan and Hydrochlorothiazide Film-Coated Tablets. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets.

Patients with severe chronic heart failure or other conditions with stimulation of the renin-angiotensin-aldosterone-system
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia, and in rare cases with acute renal failure. The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients with severe chronic heart failure has not been established.
Hence it cannot be excluded that because of the inhibition of the renin-angiotensin-aldosterone system the application of Valsartan and Hydrochlorothiazide Film-Coated Tablets as well may be associated with impairment of the renal function. Valsartan and Hydrochlorothiazide Film-Coated Tablets should not be used in these patients.

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

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with Valsartan and Hydrochlorothiazide Film-Coated Tablets as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, hypertrophic obstructive cardiomyopathy
As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).
Renal impairment
No dosage adjustment is required for patients with renal impairment with a creatinine clearance ≥30 mls/min (see section 4.2). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended when Valsartan and Hydrochlorothiazide Film-Coated Tablets are used in patients with renal impairment.

Kidney transplantation
There is currently no experience on the safe use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in patients who have recently undergone kidney transplantation.

Hepatic impairment
In patients with mild to moderate hepatic impairment without cholestasis, Valsartan and Hydrochlorothiazide Film-Coated Tablets should be used with caution (see sections 4.2 and 5.2).

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

Other metabolic disturbances
Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.
Thiazides may reduce urinary calcium excretion and cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcaemia may be evidence of underlying hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity
Cases of photosensitivity reactions have been reported with thiazides diuretics (see section 4.8). If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Pregnancy
Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in 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).

General
Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.
Anti-doping test: hydrochlorothiazide contained in this medicinal product could produce a positive analytic result in an anti-doping test.
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
Interactions related to both valsartan and hydrochlorothiazide
Concomitant use not recommended
Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors and thiazide, including hydrochlorothiazide. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.
Concomitant use requiring caution

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

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

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day, and non-selective NSAIDs
NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of Valsartan and Hydrochlorothiazide Film-Coated Tablets and NSAIDs may lead to worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Interactions related to valsartan
Concomitant use not recommended
Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels
If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

No interaction
In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide. Digoxin and indomethacin could interact with the hydrochlorothiazide component of Valsartan and Hydrochlorothiazide Film-Coated Tablets (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide
Concomitant use requiring caution
Medicinal products associated with potassium loss and hypokalaemia (e.g. kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, benoxatol, penicillin G, salicylic acid and derivatives).
If these medicinal products are to be prescribed with the hydrochlorothiazide-valsartan combination, monitoring of plasma levels of potassium is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see section 4.4).

Medicinal products that could induce torsades de pointes
Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiopride, amisulpiride, tiapride, pimozide, haloperidol, droperidol)
Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketaserin, mizolastin, pentamidine, sparflowxacin, terfenadine, vincamine i.v.)
Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 4.6 Pregnancy and lactation

#### Pregnancy

**Valsartan**
The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot
be excluded. Whilst there are no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRAs therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.

AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see also section 5.3). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see also section 4.3 and 4.4).

**Hydrochlorothiazide**

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

**Lactation**

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

**Fertility**

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

**4.7 Effects on ability to drive and use machines**

No studies on the effect of Valsartan and Hydrochlorothiazide Film-Coated Tablets, on the ability to drive and use machines have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

**4.8 Undesirable effects**

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

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

**Table 1: Frequency of adverse reactions with valsartan/hydrochlorothiazide**

### Metabolism and nutrition disorders

- Uncommon
- Dehydration

### Nervous system disorders

- Very rare
- Dizziness
- Uncommon
- Parasthesia
- Not known
- Syncope

### Eye disorders
Uncommon
Vision blurred
**Ear and labyrinth disorders**
Uncommon
Tinnitus
**Vascular disorders**
Uncommon
Hypotension
**Respiratory, thoracic and mediastinal disorders**
Uncommon
Cough
Not known
Non cardiogenic pulmonary oedema
**Gastrointestinal disorders**
Very rare
Diarrhoea
**Musculoskeletal and connective tissue disorders**
Uncommon
Myalgia
Very rare
Arthralgia
**Renal and urinary disorders**
Not known
Impaired renal function
**General disorders and administration site conditions**
Uncommon
Fatigue
**Investigations**
Not known
Serum uric acid increased, Serum bilirubin and Serum creatinine increased, Hypokalaemia, Hyponatraemia, Elevation of Blood Urea Nitrogen, Neutropenia

**Additional information on the individual components**
Adverse reactions previously reported with one of the individual components may be potential undesirable effects with Valsartan and Hydrochlorothiazide Film-Coated Tablets as well, even if not observed in clinical trials or during postmarketing period.

**Table 2: Frequency of adverse reactions with Valsartan**

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

**Renal and urinary disorders**
Not known
Renal failure

Table 3: Frequency of adverse reactions with hydrochlorothiazide

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

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

**Immune system disorders**
Very rare
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
Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

**Reproductive system and breast disorders**
Common
Impotence

### 4.9 Overdose

**Symptoms**
Overdose with valsartan may result in marked hypotension, which could lead to depressed level of consciousness, circulatory collapse and/or shock. In addition, the following signs and symptoms may occur due to an overdose of the hydrochlorothiazide component: nausea, somnolence, hypovolaemia, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment
The therapeutic measures depend on the time of ingestion and the type and severity of the symptoms, stabilisation of the circulatory condition being of prime importance. If hypotension occurs, the patient should be placed in the supine position and salt and volume supplementation should be given rapidly. Valsartan cannot be eliminated by means of haemodialysis because of its strong plasma binding behaviour whereas clearance of hydrochlorothiazide will be achieved by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics.
ATC code: C09D A03.

In a double-blind, randomised, active-controlled trial in patients not adequately controlled on valsartan 320 mg, significantly greater mean systolic/diastolic BP reductions were observed with both the combination of valsartan/hydrochlorothiazide 320/25 mg (15.4/10.4 mmHg) and valsartan/hydrochlorothiazide 320/12.5 mg (13.6/9.7 mmHg) compared to valsartan 320 mg (6.1/5.8 mmHg). The difference in systolic BP reduction between the 320/25 mg and 320/12.5 mg doses also reached statistical significance. In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (75%) and 320/12.5 mg (69%) compared to valsartan 320 mg (53%).

In a double-blind, randomised, placebo-controlled, factorial design trial comparing various dose combinations of valsartan/hydrochlorothiazide to their respective components, significantly greater mean systolic/diastolic BP reductions were observed with the combination of valsartan/hydrochlorothiazide 320/12.5 mg (21.7/15.0 mmHg) and 320/25 mg (24.7/16.6 mmHg) compared to placebo (7.0/5.9 mmHg) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (11.1/9.0 mmHg), hydrochlorothiazide 25 mg (14.5/10.8 mmHg) and valsartan 320 mg (13.7/11.3 mmHg). In addition, a significantly greater percentage of patients responded (diastolic BP <90 mmHg or reduction ≥10 mmHg) with valsartan/hydrochlorothiazide 320/25 mg (85%) and 320/12.5 mg (83%) compared to placebo (45%) and the respective monotherapies, i.e., hydrochlorothiazide 12.5 mg (60%), hydrochlorothiazide 25 mg (66%), and valsartan 320 mg (69%).

Dose-dependent decreases in serum potassium occurred in controlled clinical studies with valsartan + hydrochlorothiazide. Reduction in serum potassium occurred more frequently in patients given 25 mg hydrochlorothiazide than in those given 12.5 mg hydrochlorothiazide. In controlled clinical trials with valsartan/hydrochlorothiazide the potassium lowering effect of hydrochlorothiazide was attenuated by the potassium-sparing effect of valsartan.

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.

Valsartan
Valsartan is an orally active and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000-fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan 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) lower in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9%).
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

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).

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 2–4 weeks and is sustained 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 Diovan 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 randomised 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.

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

**5.2 Pharmacokinetic properties**

**Valsartan/hydrochlorothiazide**

The systemic availability of hydrochlorothiazide is reduced by about 30% when co-administered with valsartan. The kinetics of valsartan 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 active substance given alone, or placebo.

**Valsartan**

**Absorption**

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (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 biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

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

Hydrochlorothiazide

Absorption
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. Absolute bioavailability of hydrochlorothiazide is 60–80% after oral administration. Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has minimal clinical importance. 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.

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

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

Special populations

Elderly
A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; 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 Valsartan and Hydrochlorothiazide Film-Coated Tablets no dose adjustment is required for patients with a creatinine clearance of 30–70 ml/min. In patients with severe renal impairment (creatinine clearance <30 ml/min) and patients undergoing dialysis no data are available for Valsartan and Hydrochlorothiazide Film-Coated Tablets. 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 was increased approximately 2-fold compared with healthy volunteers. There is no data available on the use of valsartan in patients with severe hepatic dysfunction (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/day valsartan + 9 mg/kg/day hydrochlorothiazide in rats and 10 + 3 mg/kg/d in marmosets), probably by way of altered renal haemodynamics. These doses in rat, respectively, represent 0.9 and 3.5–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.3 and 1.2–times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

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). These doses in rat, respectively, represent 3.0 and 12 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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 arterioles (at 600 + 188 mg/kg/d in rats and from 30 + 9 mg/kg/d in marmosets). These doses in marmoset, respectively, represent 0.9 and 3.5 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient).

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.

In rats, maternally toxic doses of valsartan (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). Similar findings were seen with valsartan/hydrochlorothiazide in rats and rabbits. In embryo-fetal development (Segment II) studies with valsartan/hydrochlorothiazide in rat and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed.

**Paediatric population**

Daily oral dosing of neonatal/juvenile rats (from a postnatal day 7 to postnatal day 70) with valsartan at doses as low as 1 mg/kg/day (about 10-35% of the maximum recommended paediatric dose of 4 mg/kg/day on systemic exposure basis) produced persistent, irreversible kidney damage. These effects above mentioned represent an expected exaggerated pharmacological effect of angiotensin converting enzyme inhibitors and angiotensin II type 1 blockers; such effects are observed if rats are treated during the first 13 days of life. This period coincides with 36 weeks of gestation in humans, which could occasionally extend up to 44 weeks after conception in humans. The rats in the juvenile valsartan study were dosed up to day 70, and effects on renal maturation (postnatal 4-6 weeks) cannot be excluded. Functional renal maturation is an ongoing process within the first year of life in humans. Consequently, a clinical relevance in children <1 year of age cannot be excluded, while preclinical data do not indicate a safety concern for children older than 1 year.

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### PHARMACEUTICAL PARTICULARS

#### 6.1 List of excipients

Core:
- Lactose monohydrate
- Croscarmellose sodium
- Povidone
Magnesium stearate
Talc

Film-coat:
Hypromellose
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Valsartan and Hydrochlorothiazide 320 mg/12.5 mg Film-Coated Tablets are available in Al/OPA-Al-PVC blister packs with 28 tablets.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
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10 DATE OF REVISION OF THE TEXT
06/05/2011
Module 3

USER PACKAGE LEAFLET: INFORMATION FOR THE USER
Valsartan and Hydrochlorothiazide 80/12.5 mg Film-Coated Tablets
Valsartan and Hydrochlorothiazide 160/12.5 mg Film-Coated Tablets
Valsartan and Hydrochlorothiazide 160/25 mg Film-Coated Tablets
Valsartan and Hydrochlorothiazide 320/12.5 mg Film-Coated Tablets
Valsartan and Hydrochlorothiazide 320/25 mg Film-Coated Tablets
Valsartan/Hydrochlorothiazide

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Valsartan and Hydrochlorothiazide Film-Coated Tablets are and what they are used for
2. Before you take Valsartan and Hydrochlorothiazide Film-Coated Tablets
3. How to take Valsartan and Hydrochlorothiazide Film-Coated Tablets
4. Possible side effects
5. How to store Valsartan and Hydrochlorothiazide Film-Coated Tablets
6. Further Information

1 WHAT VALSARTAN AND HYDROCHLOROTHIAZIDE FILM-COATED TABLETS ARE AND WHAT THEY ARE USED FOR

Valsartan and Hydrochlorothiazide Film-Coated Tablets contain two active substances called valsartan and hydrochlorothiazide. Both of these substances help to control high blood pressure (hypertension).
- **Valsartan** belongs to a class of medicines known as "angiotensin II receptor antagonists", which help to control high blood pressure. Angiotensin II is a substance in the body that causes vessels to tighten, thus causing your blood pressure to increase. Valsartan works by blocking the effect of angiotensin II. As a result, blood vessels relax and blood pressure is lowered.
- **Hydrochlorothiazide** belongs to a group of medicines called thiazide diuretics (also known as "water tablets"). Hydrochlorothiazide increases urine output, which also lowers blood pressure.

Valsartan and Hydrochlorothiazide Film-Coated Tablets are used to treat high blood pressure which is not adequately controlled either by valsartan or hydrochlorothiazide alone.

High blood pressure increases the workload of the heart and arteries. If not treated, it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure or kidney failure. High blood pressure increases the risk of heart attacks. Lowering your blood pressure to normal reduces the risk of developing these disorders or have recently taken any other medicines, including medicines obtained without a prescription.

The effect of the treatment can be influenced if Valsartan and Hydrochlorothiazide Film-Coated Tablets are taken together with certain other medicines. It may be necessary to change the dose, to take other precautions, or in some cases to stop taking one of the medicines. This especially applies to the following medicines:
- **lithium**, a medicine used to treat some types of psychiatric illness
- medicines that affect or can be affected by potassium blood levels, such as digoxin, a medicine to control the heart rhythm, some antipsychotic medicines
- medicines that may increase the amount of potassium in your blood, such as potassium supplements, potassium-containing salt substitutes, potassium-sparing medicines, heparin
- medicines that may reduce the amount of potassium in your blood, such as corticosteroids, some laxatives
- diuretics (water tablets), medicines for the treatment of gout, such as allopurinol, therapeutic vitamin D and calcium supplements, medicines for the treatment of diabetes (oral agents or insulin)
- other medicines to lower your blood pressure, such as beta-blockers or methylxanthine, or medicines that tighten your blood vessels or stimulate your heart, such as noradrenaline or adrenaline
- medicines that may increase blood sugar levels, such as diazoxide
- medicines to treat cancer, such as methotrexate or cyclophosphamide
- pain killers
- arthritis medicines
- muscle relaxing medicines, such as tubocurarine
- anti-cholinergic medicines, such as atropine or diphenidol
- amantadine (a medicine used to prevent influenza)
- cholestyramine and colestipol (medicines used to treat high levels of fats in the blood)
- ciclosporin, a medicine used for organ transplant to avoid organ rejection
- some antibiotics (tetracyclines), anaesthetics and sedatives
- carbamazepine, a medicine used to treat seizure conditions

**Taking Valsartan and Hydrochlorothiazide Film-Coated Tablets with food and drink**

You can take Valsartan and Hydrochlorothiazide Film-Coated Tablets with or without food. Avoid taking alcohol. Alcohol may make your blood pressure fall more and/or increase the risk of you becoming dizzy or feeling faint.

**Pregnancy and breast-feeding**

Ask your doctor or pharmacist for advice before taking any medicine.
- **You must tell your doctor if you think that you are (or might become) pregnant**

Your doctor will normally advise you to stop taking Valsartan and Hydrochlorothiazide Film-Coated Tablets before you become pregnant or as soon as you know you are pregnant, and will advise you to take another medicine instead of Valsartan and Hydrochlorothiazide Film-Coated Tablets. Valsartan and Hydrochlorothiazide Film-Coated Tablets are not
2. BEFORE YOU TAKE VALSARTAN AND HYDROCHLOROTHIAZIDE FILM-COATED TABLETS

Do not take Valsartan and Hydrochlorothiazide Film-Coated Tablets:
- If you are allergic (hypersensitive) to valsartan, hydrochlorothiazide, sulphonamide derivatives (substances chemically related to hydrochlorothiazide) or to any of the other ingredients of Valsartan and Hydrochlorothiazide Film-Coated Tablets.
- If you are more than 3 months pregnant (it is also better to avoid Valsartan and Hydrochlorothiazide Film-Coated Tablets in early pregnancy - see pregnancy section).
- If you have severe liver disease.
- If you have severe kidney disease.
- If you are unable to urinate.
- If you are treated with an artificial kidney.
- If the level of potassium or sodium in your blood is lower than normal, or if the level of calcium in your blood is higher than normal despite treatment.
- If you have gout.

If any of the above apply to you, do not take this medicine and speak to your doctor.

Take special care with Valsartan and Hydrochlorothiazide Film-Coated Tablets:
- If you are taking potassium-sparing medicines, potassium supplements, salt substitutes containing potassium or other medicines that increase the amount of potassium in your blood such as heparin.
- Your doctor may need to check the amount of potassium in your blood regularly.
- If you have low levels of potassium in your blood.
- If you have diarrhoea or severe vomiting.
- If you are taking high doses of water tablets (diuretics).
- If you have severe heart disease.
- If you suffer from a narrowing of the kidney artery.
- If you have recently received a new kidney.
- If you suffer from hyperaldosteronism. This is a disease in which your adrenal glands make too much of the hormone aldosterone. If this applies to you, the use of Valsartan and Hydrochlorothiazide Film-Coated Tablets is not recommended.
- If you have liver or kidney disease.
- If you have fever, rash and joint pain, which may be signs of systemic lupus erythematosus (SLE, a so-called autoimmune disease).
- If you have diabetes, gout, high levels of cholesterol or fats in your blood.
- If you have allergic reactions with the use of other blood pressure-lowering agents of this class (angiotensin II receptor antagonists) or if you have allergy or asthma.
- It may cause increased sensitivity of the skin to sun.

The use of Valsartan and Hydrochlorothiazide Film-Coated Tablets in children and adolescents (below the age of 18 years) is not recommended.

You must tell your doctor if you think you are (or might become) pregnant. Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage (see pregnancy section).

The hydrochlorothiazide contained in this medicine could produce a positive result in an anti-doping test.

Taking other medicines
Please tell your doctor or pharmacist if you are taking

recommendations in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby.

Tell your doctor if you are breast-feeding or about to start breast-feeding
Valsartan and Hydrochlorothiazide Film-Coated Tablets are not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines
Before you drive a vehicle, use tools, operate machines or carry out other activities that require concentration, make sure you know how Valsartan and Hydrochlorothiazide Film-Coated Tablets affect you. Like many other medicines used to treat high blood pressure, Valsartan and Hydrochlorothiazide Film-Coated Tablets may occasionally cause dizziness and affect the ability to concentrate.

Important information about some of the ingredients of Valsartan and Hydrochlorothiazide Film-Coated Tablets
Valsartan and Hydrochlorothiazide Film-Coated Tablets contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE VALSARTAN AND HYDROCHLOROTHIAZIDE FILM-COATED TABLETS

Always take Valsartan and Hydrochlorothiazide Film-Coated Tablets exactly as your doctor has told you. This will help you to get the best results and lower the risk of side effects. You should check with your doctor or pharmacist if you are not sure.

People with high blood pressure often do not notice any signs of this problem. Many may feel quite normal. This makes it all the more important for you to keep your appointments with your doctor even if you are feeling well.

Your doctor will tell you exactly how many tablets of Valsartan and Hydrochlorothiazide Film-Coated Tablets to take. Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

- The usual dose of Valsartan and Hydrochlorothiazide Film-Coated Tablets is one tablet per day.
- Do not change the dose or stop taking the tablets without consulting your doctor.
- The medicine should be taken at the same time each day, usually in the morning.
- You can take Valsartan and Hydrochlorothiazide Film-Coated Tablets with or without food.
- Swallow the tablet with a glass of water.

If you take more Valsartan and Hydrochlorothiazide Film-Coated Tablets than you should
If you experience severe dizziness and/or fainting, lay down and contact your doctor immediately.
If you have accidentally taken too many tablets, contact your doctor, pharmacist or hospital.

If you forget to take Valsartan and Hydrochlorothiazide Film-Coated Tablets
If you forget to take a dose, take it as soon as you remember. However, if it is almost time for your next dose, skip the dose you missed.

Do not take a double dose to make up for a forgotten dose.
If you stop taking Valsartan and Hydrochlorothiazide Film-Coated Tablets

Stopping your treatment with Valsartan and Hydrochlorothiazide Film-Coated Tablets may cause your high blood pressure to get worse. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Valsartan and Hydrochlorothiazide Film-Coated Tablets can cause side effects, although not everybody gets them.

These side effects may occur with certain frequencies, which are defined as follows:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data

Some side effects can be serious and need immediate medical attention.

You should see your doctor immediately if you experience symptoms of angioedema, such as:
- swollen face, tongue or pharynx
- difficulty in swallowing
- hives and difficulties in breathing

Other side effects include:

Uncommon
- cough
- low blood pressure
- light-headedness
- dehydration (with symptoms of thirst, dry mouth and tongue, infrequent urination, dark colored urine, dry skin)
- muscle pain
- tiredness
- tingling or numbness
- blurred vision
- noises (e.g. hissing, buzzing) in ears

Very rare
- dizziness
- diarrhoea
- joint pain

Not known
- breathing difficulty
- severely decreased urine output
- low level of sodium in the blood (sometimes with nausea, tiredness, confusion, malaise, convulsions)
- low level of potassium in the blood (sometimes with muscle weakness, muscle spasms, abnormal heart rhythm)
- low level of white cells in the blood (with symptoms such as fever, skin infections, sore throat or mouth ulcers due to infections, weakness)
- the level of bilirubin increased in blood (which can, in severe cases, trigger yellow skin and eyes)
- the level of blood urea nitrogen and creatinine increased in blood (which can indicate abnormal kidney function)
- the level of uric acid in blood increased (which can, in severe cases, trigger gout)
- syncope (fainting)

storage conditions.
- Keep out of the reach and sight of children.
- Do not use Valsartan and Hydrochlorothiazide Film-Coated Tablets after the expiry date which is stated on the pack. The expiry data refers to the last day of that month.
- Do not use any Valsartan and Hydrochlorothiazide Film-Coated Tablets pack that is damaged or shows signs of tampering.
- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

5. FURTHER INFORMATION

What Valsartan and Hydrochlorothiazide Film-Coated Tablets contain

The active substances are: valsartan and hydrochlorothiazide.

One film-coated tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.

One film-coated tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.

One film-coated tablet contains 320 mg of valsartan and 25 mg of hydrochlorothiazide.

The other ingredients are:
Core: lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, talc.

Film-coat:
Valsartan and Hydrochlorothiazide 80 mg/12.5 mg

Film-Coated Tablets:
Hyppromellose, titanium dioxide, macrogol 400
Valsartan and Hydrochlorothiazide 160 mg/12.5 mg

Film-Coated Tablets:
Hyppromellose, titanium dioxide (E 171), macrogol 400, ferric oxide red (E 172)

Valsartan and Hydrochlorothiazide 160 mg/25 mg

Film-Coated Tablets:
Hyppromellose, titanium dioxide (E 171), macrogol 400, ferric oxide yellow (E 172)

Valsartan and Hydrochlorothiazide 320 mg/12.5 mg

Film-Coated Tablets:
Hyppromellose, titanium dioxide (E 171), macrogol 400, ferric oxide red (E 172)

Valsartan and Hydrochlorothiazide 320 mg/25 mg

Film-Coated Tablets:
Hyppromellose, titanium dioxide (E 171), macrogol 400

What Valsartan and Hydrochlorothiazide Film-Coated Tablets look like and contents of the pack

Valsartan and Hydrochlorothiazide 80 mg/12.5 mg

Film-Coated Tablets are white to off white, oval shaped, bevelled edge, biconvex film coated tablets debossed with “1071” on one side and plain on the other side.

Valsartan and Hydrochlorothiazide 80 mg/12.5 mg

Film-Coated Tablets are available in Al/OPA-Al/PVC blister packs with 28 tablets.

Valsartan and Hydrochlorothiazide 160 mg/12.5 mg

Film-Coated Tablets are pink coloured, oval shaped, bevelled edge, biconvex film coated tablets debossed
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

Side effects reported with valsartan or hydrochlorothiazide alone, but not observed with Valsartan and Hydrochlorothiazide Film-Coated Tablets:

**Valsartan**
- uncommon
  - spinning sensation
  - abdominal pain

**Not known**
- skin rash with or without itching together with some of the following signs or symptoms: fever, joint pain, muscle pain, swollen lymph nodes and/or flu-like symptoms
- rash, purplish-red spots, fever, itching (symptoms of inflammation of blood vessels)
- low level of blood platelets (sometimes with unusual bleeding or bruising)
- high level of potassium in the blood (sometimes with muscle spasms, abnormal heart rhythm)
- allergic reactions (with symptoms such as rash, itching, hives, difficulty breathing or swallowing, dizziness)
- swelling mainly of the face and throat; rash; itching
- elevation of liver function values
- the level of haemoglobin decreased and the percentage of red cells decreased in the blood (which both can, in severe cases, trigger an anaemia).
- kidney failure

**Hydrochlorothiazide**

**Common**
- itchy rash and other types of rash
- reduced appetite
- mild nausea and vomiting
- faintness, fading on standing up
- impotence.

**Rare**
- swelling and blistering of the skin (due to increased sensitivity to sun)
- constipation, discomfort of the stomach or bowels, liver disorders (yellow skin or eyes)
- irregular heart beat
- headache
- sleep disturbances
- sad mood (depression)
- low level of blood platelets (sometimes with bleeding or bruising underneath the skin).

**Very rare**
- inflammation of blood vessels with symptoms such as rash, purplish-red spots, fever
- itching or red skin
- blistering of the lips, eyes or mouth
- skin peeling
- fever
- facial rash associated with joint pain
- muscle disorder
- fever (cutaneous lupus erythematosus)
- severe upper stomach pain; lack or low levels of different blood cells
- severe allergic reactions
difficulty breathing
lung infection: breathlessness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Valsartan AND Hydrochlorothiazide Film-Coated Tablets

This medicinal product does not require any special storage conditions.

603/257-7943
Module 4
Labelling
Lot:

Valsartan and Hydrochlorothiazide
80 mg/12.5 mg Film-Coated Tablets

Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH

Valsartan and Hydrochlorothiazide
80 mg/12.5 mg Film-Coated Tablets

Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH

Valsartan and Hydrochlorothiazide
80 mg/12.5 mg Film-Coated Tablets

Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

UK/H/3712/001-5/DC

Valsartan and Hydrochlorothiazide
160 mg/12.5 mg Film-Coated Tablets

Each film-coated tablet contains 160 mg valsartan and 12.5 mg hydrochlorothiazide.

Contains lactose.

Oral use.

Notify package holder before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Lot:

Valsartan and Hydrochlorothiazide
160 mg/25 mg Film-Coated Tablets
Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH

Valsartan and Hydrochlorothiazide
160 mg/25 mg Film-Coated Tablets
Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH

Valsartan and Hydrochlorothiazide
160 mg/25 mg Film-Coated Tablets
Valsartan + Hydrochlorothiazide

Torrent Pharma GmbH
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets

Valsartan and Hydrochlorothiazide
320 mg/12.5 mg Film-Coated Tablets

Each film-coated tablet contains 320 mg valsartan and 12.5 mg hydrochlorothiazide.
Contains lactose.
Oral use.
Read the package leaflet before use.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Torrent

UK/H/3712/001-5/DC
VALSARTAN and HYDROCHLOROTHIAZIDE 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-Coated Tablets

UK/H/3712/001-5/DC
PAR Valsartan and Hydrochlorothiazide 80/12.5mg, 160/12.5mg, 160/25mg, 320/12.5mg and 320/25mg Film-coated Tablets
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Valsartan and Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg Film-Coated Tablets in the treatment of essential hypertension in adults., could be approved.

These applications were submitted under Article 10.1 (for Valsartan and Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg and 160 mg/25 mg Film-Coated Tablets) and Article 10.3 (for Valsartan and Hydrochlorothiazide 320 mg/12.5 mg and 320 mg/25 mg Film-Coated Tablets), claiming to be either generic medicinal products or a hybrid medicinal products of Co-Diovan® 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg Film-Coated Tablets (PL 00101/0480, 0650-1), which were first licensed to Novartis Pharmaceuticals UK Ltd, on 29th January 2003 and 23rd June 2004 respectively.

With the UK as the RMS in these Decentralised Procedures (UK/H/3712/001-5/DC), Torrent Pharma GmbH, applied for Marketing Authorisations for Valsartan and Hydrochlorothiazide 80 mg/12.5 mg, 160 mg/12.5 mg, 160 mg/25 mg, 320 mg/12.5 mg and 320 mg/25 mg Film-Coated Tablets in Germany, Italy, Lithuania and Romania.

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

Hydrochlorothiazide is thiazide diuretic and has been in use for more than 30 years in the treatment of hypertension. 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 transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na+Cl- symporter perhaps by competing for the Cl- site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly by this diuretic action reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so with co-administration of valsartan the reduction in serum potassium is less pronounced as observed under monotherapy with hydrochlorothiazide.

No new preclinical and clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products/hybrid of originator products that have been licensed for over 10 years. Bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).
The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All Member States agreed to grant a licence for the above products at the end of procedure (Day 210 – 6th April 2011). After a subsequent national phase, the UK granted a licence for these products on 6th May 2011 (PL 20658/0037-40, 48).
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Valsartan and Hydrochlorothiazide 80 mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>valsartan and hydrochlorothiazide</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>C09CA03 - angiotensin II antagonists, combinations, angiotensin II antagonists and diuretics</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>80 mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg Film-Coated Tablets</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedures</td>
<td>UK/H/3712/001-5/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Germany, Italy, Lithuania and Romania</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20658/0037-40, 48</td>
</tr>
</tbody>
</table>
| Name and address of the authorisation holder     | Torrent Pharma GmbH  
Suedwestpark 50  
90449 Nuremberg  
Germany                                                                }|
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Valsartan
Chemical Name: N-(1-Oxypentyl)-N-[[2-(1H-tetrazole-5-yl)phenyl]phenylmethyl]-L-valine

Structure:

\[
\text{\begin{center}
\begin{array}{c}
\text{H} \\
\text{N} \quad \text{N} \\
\text{H} \quad \text{N} \\
\end{array}
\end{center}
\]

Molecular Formula: C_{24}H_{29}N_{5}O_{3}
Molecular Weight: 435.5
Appearance: is a white or almost white crystalline powder.
Solubility: It is freely soluble in methanol and ethanol, sparingly soluble in ethyl acetate, slightly soluble in dichloromethane and practically insoluble in water.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificates of Analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

INN: Hydrochlorothiazide
Chemical Name: 6-Chloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4-benzothiadiazine-1,1-dioxide
Structure:

Molecular Formula: C\textsubscript{7}H\textsubscript{8}N\textsubscript{5}O\textsubscript{3} ClN\textsubscript{3}O\textsubscript{4}S\textsubscript{2}

Molecular Weight: 297.75

Appearance: is a white or almost white crystalline powder.

Solubility: It is slightly soluble in water, soluble in acetone, sparingly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

**DRUG PRODUCT**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, croscarmellose, sodium, povidone, magnesium stearate, talc, hypromellose, titanium dioxide (E171) and macrogol 400, ferric oxide yellow (E172) (for 160mg/25mg) and ferric oxide red (E172) (for 160mg/12.5 and 320mg/25mg).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of ferric oxide yellow (E172) and ferric oxide red (E172) which comply with the United States Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has confirmed that the excipients are not manufactured using any material of animal origin and therefore contain no TSE/BSE risk.

**Pharmaceutical Development**

The objective of the development programme was to formulate robust, stable tablets that contain the same active ingredient as Co-Diovan Film-coated Tablets.

Comparative impurity and dissolution profiles have been presented for test and reference products.

**Manufacture**

A satisfactory batch formula has been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data were provided on batches up to 155,000 tablets for the three lower strengths and on batches up to the maximum proposed commercial scale i.e. 180,000 and 185,000 tablets for the higher strengths.
formal validation plan has been outlined on the proposed larger production batches for the lower strengths, where validation activity will be carried out on each of three batches of each batch size. The results are satisfactory.

**Finished Product Specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
The finished product is packed in Aluminium/OPA-AL-PVC blister packs with a pack size of 28, 56 or 98 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years with no special storage conditions is set. This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labels are pharmaceutically acceptable.

User testing of the package leaflet has been accepted, based on a bridging report provided by the applicant making reference to the user-testing of the PIL for Valsartan Comp. Torrent 320mg/25mg as the parent PIL. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification on the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**
There are no objections to the approval of these products from a pharmaceutical point of view.
III.2 PRE-CLINICAL ASPECTS
Pharmacodynamic, pharmacokinetic and toxicological properties of valsartan and hydrochlorothiazide are well known. As valsartan and hydrochlorothiazide are widely used and well-known, the applicant has not provided additional studies in support of their application. Overview based on literature review is, thus, appropriate.

No new preclinical data have been supplied with these applications and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of environmental risk assessment.

There are no objections to the approval of these products from a preclinical point of view.

III.3 CLINICAL ASPECTS
Clinical Pharmacology
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted three bioequivalence studies PK-08-053 (160/25mg tablets), PK-08-054 (320/12.5mg tablets) and PK-08-055 (320/25mg Tablets) under fasting conditions.

Study 1 (PK-08-053)
This is an open, randomised, two-period, two-treatment, single dose, crossover bioavailability study of Valsartan and Hydrochlorothiazide 160mg/25mg film-coated tablets and (test) and Co-Diovan Forte 160mg/25mg film-coated tablets (reference) in healthy male volunteers under fasting conditions.

Nineteen blood samples were collected at the following time points; prior to study drug administration (i.e. Pre-dose), 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 9.0, 12.0, 18.0, 24.0, 36.0 and 48.0 hours post dose in each period. Washout period of 7 days was kept between two periods.

Results
Table 1. 90% Confidence Interval for Valsartan (n=39)

<table>
<thead>
<tr>
<th>PK Parameters (N=39)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ln}(C_{\text{max}}) )</td>
<td>85.25-121.25</td>
<td>101</td>
<td>48.63%</td>
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<tr>
<td>( \text{Ln}(AUC_{\text{last}}) )</td>
<td>82.79-113.06</td>
<td>96.75</td>
<td>42.51%</td>
</tr>
<tr>
<td>( \text{Ln}(AUC_{\text{inf}}) )</td>
<td>84.05-112.87</td>
<td>97.40</td>
<td>40.04%</td>
</tr>
</tbody>
</table>

Table 2. 90% Confidence Interval for Hydrochlorothiazide (n=39)

<table>
<thead>
<tr>
<th>PK Parameters (N=39)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ln}(C_{\text{max}}) )</td>
<td>95.02-113.13</td>
<td>103.68</td>
<td>23.12%</td>
</tr>
<tr>
<td>( \text{Ln}(AUC_{\text{last}}) )</td>
<td>89.87-106.44</td>
<td>97.80</td>
<td>22.40%</td>
</tr>
<tr>
<td>( \text{Ln}(AUC_{\text{inf}}) )</td>
<td>90.17-106.02</td>
<td>97.77</td>
<td>21.42%</td>
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</tbody>
</table>
Study 2 (PK-08-054)
This is an open, randomised, two-period, two-treatment, single dose, crossover bioavailability study of Valsartan and Hydrochlorothiazide 320mg/12.5mg tablets and (test) and Co-Diovan Forte 320mg/12.5mg tablets (reference) in healthy male volunteers under fasting conditions.

Table 3. 90% Confidence Interval for Valsartan (n=36)

<table>
<thead>
<tr>
<th>PK Parameters (N=39)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>91.46-106.17</td>
<td>98.54</td>
<td>18.88</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;last&lt;/sub&gt;)</td>
<td>92.52-105.10</td>
<td>98.61</td>
<td>16.10</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;inf&lt;/sub&gt;)</td>
<td>92.66-105.14</td>
<td>98.71</td>
<td>15.94</td>
</tr>
</tbody>
</table>

Table 4. 90% Confidence Interval for Hydrochlorothiazide (n=36)

<table>
<thead>
<tr>
<th>PK Parameters (N=39)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>86.98-97.92</td>
<td>92.29</td>
<td>14.95</td>
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<tr>
<td>Ln(AUC&lt;sub&gt;last&lt;/sub&gt;)</td>
<td>89.90-100.19</td>
<td>94.91</td>
<td>13.66</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;inf&lt;/sub&gt;)</td>
<td>90.69-100.58</td>
<td>95.51</td>
<td>13.04</td>
</tr>
</tbody>
</table>

Study 3 (PK-08-055)
This is an open, randomised, two-period, two-treatment, single dose, crossover bioavailability study of Valsartan and Hydrochlorothiazide 320mg/25mg tablets and (test) and Co-Diovan Forte 320mg/25mg tablets (reference) in healthy male volunteers under fasting conditions.

Table 5. 90% Confidence Interval for Valsartan (n=35)

<table>
<thead>
<tr>
<th>PK Parameters (N=35)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>94.38-120.19</td>
<td>106.51</td>
<td>30.54%</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;last&lt;/sub&gt;)</td>
<td>98.14-119.42</td>
<td>108.26</td>
<td>24.60%</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;inf&lt;/sub&gt;)</td>
<td>98.25-119.19</td>
<td>108.22</td>
<td>24.21%</td>
</tr>
</tbody>
</table>

Table 6. 90% Confidence Interval for Hydrochlorothiazide (n=35)

<table>
<thead>
<tr>
<th>PK Parameters (N=35)</th>
<th>90% Confidence Interval (Lower limit-Upper limit)</th>
<th>Geometric LSM Ratio (%) (Test/Reference)</th>
<th>Intra Subject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln(C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>95.68-112.46</td>
<td>103.73</td>
<td>20.16%</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;last&lt;/sub&gt;)</td>
<td>99.57-111.43</td>
<td>105.33</td>
<td>13.97%</td>
</tr>
<tr>
<td>Ln(AUC&lt;sub&gt;inf&lt;/sub&gt;)</td>
<td>100.83-112.36</td>
<td>106.44</td>
<td>13.44%</td>
</tr>
</tbody>
</table>
The 90% confidence intervals for C_{max} and AUC were within the pre-defined limits (80-125%). Bioequivalence has been shown for the test formulations (Valsartan and Hydrochlorothiazide 160mg/25mg, 320mg/12.5mg and 320mg/25mg Tablets) and the reference formulation (Co-Diovan Forte 160mg/25mg, 320mg/12.5mg and 320mg/25mg Tablets). Satisfactory justification is provided for a bio-waiver according to the Committee for Proprietary Medicinal Products Notes for Guidance on “Guideline on the Investigation of Bioequivalence” (CHMP/EWP/QWP/1401/98 Rev.1 Corr**). The results of the study for 160mg/25mg and 320mg/25mg formulation can therefore be extrapolated to the other strengths i.e 80mg/12.5mg and 160mg/12.5mg Tablets.

**Pharmacodynamics**
No new data have been submitted and none are required for these generic applications.

**Clinical Efficacy**
No new data have been submitted and none are required.

**Clinical Safety**
No new data have been submitted and none are required.

**Expert Report**
A clinical overall summary, written by an appropriately qualified physician, has been provided. This is a satisfactory, non-critical summary of Module 5.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the reference products.

**Clinical Expert Report**
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Marketing Authorisation Application (MAA) Forms**
The MAA forms are medically satisfactory.

**Clinical Conclusion**
There are no objections to the approval of these products from a clinical point of view.
IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Valsartan and Hydrochlorothiazide 80mg/12.5mg, 160mg/12.5mg, 160mg/25mg, 320mg/12.5mg and 320mg/25mg Film-Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence have been demonstrated between the applicant’s Valsartan and Hydrochlorothiazide 160mg/25mg and 320mg/12.5mg and 320mg/25mg Film-Coated Tablets and the reference products, Co-Diovan Forte 160mg/25mg, 320mg/12.5mg and 320mg/25mg Tablets and the results of the study for 160mg/25mg and 320mg/25mg formulations can therefore be extrapolated to the other strengths i.e 80mg/12.5mg and 160mg/12.5mg Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with valsartan and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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