

1. NAME OF THE MEDICINAL PRODUCT

Valsartan/Hydrochloorthiazide Viatris 80 mg/12.5 mg, filmomhulde tabletten
 Valsartan/Hydrochloorthiazide Viatris 160 mg/12.5 mg, filmomhulde tabletten
 Valsartan/Hydrochloorthiazide Viatris 160 mg/25 mg, filmomhulde tabletten
 Valsartan/Hydrochloorthiazide Viatris 320 mg/12.5 mg filmomhulde tabletten
 Valsartan/Hydrochloorthiazide Viatris 320 mg/25 mg filmomhulde tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Valsartan/Hydrochloorthiazide Viatris 80 mg/12.5 mg, filmomhulde tabletten

Each tablet contains 80 mg of valsartan and 12.5 mg of hydrochlorothiazide.
 Excipient with known effect: 51.950 mg of lactose monohydrate.

Valsartan/Hydrochloorthiazide Viatris 160 mg/12.5 mg, filmomhulde tabletten

Each tablet contains 160 mg of valsartan and 12.5 mg of hydrochlorothiazide.
 Excipient with known effect: 103.900 mg of lactose monohydrate.

Valsartan/Hydrochloorthiazide Viatris 160 mg/25 mg, filmomhulde tabletten

Each tablet contains 160 mg of valsartan and 25 mg of hydrochlorothiazide.
 Excipient with known effect: 103.900 mg of lactose monohydrate.

Valsartan/Hydrochloorthiazide Viatris 320 mg/12.5 mg filmomhulde tabletten

Each tablet contains 320 mg of valsartan and 12.5 mg of hydrochlorothiazide.
 Excipient with known effect: 207.800 mg of lactose monohydrate

Valsartan/Hydrochloorthiazide Viatris 320 mg/25 mg filmomhulde tabletten

Each tablet contains 320 mg of valsartan and 25 mg of hydrochlorothiazide.
 Excipient with known effect: 207.800 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Valsartan/Hydrochloorthiazide Viatris 80 mg/12.5 mg, filmomhulde tabletten

Peach, oval, biconvex film-coated tablet (12.5 x 6.4 mm) debossed with “VH1” on one side of the tablet and “M” on other side.

Valsartan/Hydrochloorthiazide Viatris 160 mg/12.5 mg, filmomhulde tabletten

Reddish, oval, biconvex film-coated tablet (16.1 x 7.6 mm) debossed with “VH2” on one side of the tablet and “M” on other side.

Valsartan/Hydrochloorthiazide Viatriis 160 mg/25 mg, filmomhulde tabletten

Brown, oval, biconvex film-coated tablet (16.1 x 7.6 mm) debossed with “VH3” on one side of the tablet and “M” on other side.

Valsartan/Hydrochloorthiazide Viatriis 320 mg/12.5 mg filmomhulde tabletten

Pink, oval, biconvex film-coated tablet (21.1 x 10.7 mm) debossed with “VH4” on one side of the tablet and “M” on other side.

Valsartan/Hydrochloorthiazide Viatriis 320 mg/25 mg filmomhulde tabletten

Yellow, oval, biconvex film-coated tablet (21.1 x 10.7 mm) debossed with “VH5” on one side of the tablet and “M” on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in adults.

Valsartan/Hydrochloorthiazide Viatriis 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/Hydrochloorthiazide Viatriis 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/Hydrochloorthiazide Viatriis 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/Hydrochloorthiazide Viatriis 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.

Method of administration

Valsartan/Hydrochloorthiazide Viatris tablets can be taken with or without food and should be administered with water.

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

Special populations

Renal Impairment

No dose adjustment is required for patients with mild to moderate renal impairment (Glomerular Filtration Rate (GFR) ≥ 30 ml/min). Due to the hydrochlorothiazide component, Valsartan/Hydrochloorthiazide Viatris is contraindicated in patients with severe renal impairment (GFR < 30 ml/min) and anuria (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). No adjustment of the hydrochlorothiazide dose is required for patients with mild to moderate hepatic impairment. Due to the valsartan component, Valsartan/Hydrochloorthiazide Viatris is contraindicated in patients with severe hepatic impairment or with biliary cirrhosis and cholestasis (see sections 4.3, 4.4 and 5.2).

Elderly

No dose adjustment is required in elderly patients.

Paediatric population

Valsartan/Hydrochloorthiazide Viatris is 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 the active substances, other sulfonamide-derived medicinal products or to any of the excipients listed in section 6.1.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Severe renal impairment (creatinine clearance < 30 ml/min), anuria.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- The concomitant use of Valsartan/Hydrochloorthiazide Viatris with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Valsartan/Hydrochloorthiazide Viatris should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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 hypochloraemic 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/Hydrochlorothiazide Viatriis. Sodium and/or volume depletion should be corrected before starting treatment with Valsartan/Hydrochlorothiazide Viatriis.

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 and/or death. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function. The use of Valsartan/Hydrochlorothiazide Viatriis 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/Hydrochlorothiazide Viatriis as well may be associated with impairment of the renal function. Valsartan/Hydrochlorothiazide Viatriis should not be used in these patients.

Renal artery stenosis

Valsartan/Hydrochlorothiazide Viatriis 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/Hydrochlorothiazide Viatriis 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/Hydrochlorothiazide Viatriis is used in patients with renal impairment.

Kidney transplantation

There is currently no experience on the safe use of Valsartan/Hydrochlorothiazide Viatriis in patients who have recently undergone kidney transplantation.

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, Valsartan/Hydrochlorothiazide Viatriis should be used with caution (see sections 4.2 and 5.2). Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

History of angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported in patients treated with valsartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors.

Valsartan/Hydrochlorothiazide Viatriis should be immediately discontinued in patients who develop angioedema, and Valsartan/Hydrochlorothiazide Viatriis should not be re-administered (see section 4.8).

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including valsartan] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, valsartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as

limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

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 thiazide 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.

Choroidal effusion, acute myopia and acute Angle-closure glaucoma

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

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

The use of aliskiren in combination with Valsartan/Hydrochlorothiazide Viatris is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see section 4.3).

Excipients

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

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists or thiazide, including hydrochlorothiazide. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with Valsartan/Hydrochlorothiazide Viatris. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution***Other antihypertensive agents***

Valsartan/Hydrochlorothiazide Viatris may increase the effects of other agents with antihypertensive properties (e.g. guanethidine, methyldopa, vasodilators, ACEI, ARBs, beta-blockers, calcium channel blockers, DRIs).

Pressor amines (e.g. noradrenaline, adrenaline)

Possible decreased response to pressor amines. The clinical significance of this effect is uncertain and 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/Hydrochlorothiazide Viatris 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

Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS) with ARBs, ACEIs, or aliskiren

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

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.

Transporters

In vitro data indicates that valsartan is a substrate of the hepatic uptake transporter OATP1B1/OATP1B3 and the hepatic efflux transporter MRP2. The clinical relevance of this finding is unknown. Co-administration of inhibitors of the uptake transporter (eg. rifampin, ciclosporin) or efflux transporter (eg. ritonavir) may increase the systemic exposure to valsartan. Exercise appropriate care when initiating or ending concomitant treatment with such drugs.

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/Hydrochlorothiazide Viatris (see interactions related to hydrochlorothiazide).

Interactions related to hydrochlorothiazide

Concomitant use requiring caution

Medicinal products affecting serum potassium level

The hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, ACTH, amphotericin, carbenoxolone, penicillin G, salicylic acid and derivatives.

If these medicinal products are to be prescribed with the valsartan-hydrochlorothiazide combination, monitoring of potassium plasma levels is advised (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, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

- Others (e.g. bepridil, cisapride, diphemanil, erythromycin i.v., halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacin, 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, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.

Medicinal products affecting serum sodium level

The hyponatraemic effect of diuretics may be intensified by concomitant administration of drugs such as antidepressants, antipsychotics, antiepileptics, etc. Caution is advised in long-term administration of these drugs.

Digitalis glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects favouring the onset of digitalis-induced cardiac arrhythmias (see section 4.4).

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. Concomitant use of thiazide type diuretics with calcium salts may cause hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D mediated conditions) by increasing tubular calcium reabsorption.

Antidiabetic agents (oral agents and insulin)

Thiazides may alter 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) and other medicinal products affecting gastric motility

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. Conversely, it is anticipated that prokinetic drugs such as cisapride may decrease the bioavailability of thiazide-type diuretics.

Amantadine

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

Ion exchange resins

Absorption of thiazide diuretics, including hydrochlorothiazide is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 h before or 4-6 h after the administration of resins would potentially minimise the interaction.

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 skeletal muscle relaxants such as curare derivatives.

Ciclosporin

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

Alcohol, barbiturates or narcotics

Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilation) may potentiate orthostatic hypotension.

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 Fertility, 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 is 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 sections 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 foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Breast-feeding

No information is available regarding the use of valsartan during breast-feeding.

Hydrochlorothiazide is excreted in human milk. Therefore the use of **Valsartan/Hydrochlorothiazide Viatriis** 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.

4.7 Effects on ability to drive and use machines

No studies on the effect of **Valsartan/Hydrochlorothiazide Viatriis**, 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 post-marketing reports are presented below according to system organ class. Adverse reactions known to occur with each component given individually but which have not been seen in clinical trials may occur during treatment with valsartan/hydrochlorothiazide.

Adverse drug reactions are ranked by frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); 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

	Common	Uncommon	Rare	Very Rare	Not known
Metabolism and nutrition disorders		Dehydration			
Nervous system disorders		Paraesthesia		Dizziness	Syncope
Eye disorders		Vision blurred			
Ear and labyrinth disorders		Tinnitus			
Vascular disorders		Hypotension			
Respiratory, thoracic and mediastinal disorders		Cough			Non cardiogenic pulmonary oedema
Gastrointestinal disorders				Diarrhoea	
Musculoskeletal and connective tissue disorders		Myalgia		Arthralgia	
Renal and urinary disorders					Impaired renal function
General disorders and administration site conditions		Fatigue			
Investigations					Increased serum uric acid, increased serum bilirubin and serum creatinine, 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/Hydrochlorothiazide Viatriis as well, even if not observed in clinical trials or during post-marketing period.

Table 2. Frequency of adverse reactions with valsartan

	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders					Decrease in haemoglobin, decrease in haematocrit, thrombocytopenia
Immune system disorders					Other hypersensitivity /allergic reactions including serum sickness
Metabolism and nutrition disorders					Increase in serum potassium, hyponatraemia
Ear and labyrinth disorders		Vertigo			
Vascular disorders					Vasculitis
Gastrointestinal disorders		Abdominal pain		Intestinal angioedema	
Hepatobiliary disorders					Elevation of liver function values
Skin and subcutaneous tissue disorders					Angioedema, rash, dermatitis bullous, pruritus
Renal and urinary disorders					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/Hydrochlorothiazide Viatris. The following adverse reactions have been reported in patients treated with monotherapy of thiazide diuretics, including hydrochlorothiazide:

	Very common	Common	Uncommon	Rare	Very Rare	Not known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders				Thrombocytopenia sometimes with purpura	Agranulocytosis, leucopenia, haemolytic anaemia, bone marrow failure	Aplastic anaemia
Immune system disorders					Hypersensitivity reactions	
Metabolism and nutrition disorders	Hypokalaemia, blood lipids increased (mainly at higher doses)	Hyponatraemia, hypomagnesaemia, hyperuricaemia		Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state	Hypochloraemic alkalosis	Metabolism and nutrition disorders
Psychiatric disorders				Depression, sleep disturbances		
Nervous system disorders				Headache, dizziness, paraesthesia		
Eye disorders				Visual impairment		Choroidal effusion, acute angle-closure glaucoma
Cardiac disorders				Cardiac arrhythmias		
Vascular disorders		Postural hypotension				

SAMENVATTING VAN PRODUCTKENMERKEN

Valsartan/HCTZ Viatris 80/12,5 mg, 160/12,5 mg, 160/25 mg, 320/125 mg en 320/25 mg, filmomhulde tabletten

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Respiratory, thoracic and mediastinal disorders					Respiratory distress including pneumonitis and pulmonary oedema Acute respiratory distress syndrome (ARDS) (see section 4.4)	
Gastrointestinal disorders		Loss of appetite, mild nausea and vomiting		Constipation, gastrointestinal discomfort, diarrhoea	Pancreatitis	
Hepatobiliary disorders				Intrahepatic cholestasis or jaundice		
Skin and subcutaneous tissue disorders		Urticaria and other forms of rash		Photosensitisation	Necrotising vasculitis and toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	Erythema multiforme
Musculoskeletal and connective tissue disorders						Muscle spasm
Renal and urinary disorders						Renal dysfunction, acute renal failure
Reproductive system and breast disorders		Impotence				
General disorders and administration site conditions						Pyrexia, asthenia

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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.

Management

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 and diuretics, valsartan and diuretics;
ATC Code: C09D A03

Valsartan/Hydrochlorothiazide

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%).

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%).

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%).

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

Mechanism of action

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.

Pharmacodynamic effect

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 ($P < 0.05$).

Clinical efficacy and safety

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.

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker. ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Hydrochlorothiazide

Mechanism of action

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.

Clinical efficacy and safety

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4).

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 (C_{max}) 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 ($t_{1/2\alpha} < 1$ 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). The increase in mean AUC is linear and dose proportional in the therapeutic range. The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution

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

Hydrochlorothiazide is eliminated predominantly as unchanged drug. Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily.

There is more than 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.

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/Hydrochlorothiazide Viatris no dose adjustment is required for patients with a Glomerular Filtration Rate (GFR) of 30-70 ml/min.

In patients with severe renal impairment (GFR <30 ml/min) and patients undergoing dialysis no data are available for Valsartan/Hydrochlorothiazide Viatris. Valsartan is highly bound to plasma protein and is not to be removed by dialysis, whereas clearance of hydrochlorothiazide will be achieved by dialysis.

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed. Hydrochlorothiazide is contraindicated in patients with severe renal impairment (see section 4.3).

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/day 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/m^2 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/m^2 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 $100 \pm 31 \text{ mg}/\text{kg}/\text{day}$ in rats and $30 \pm 9 \text{ mg}/\text{kg}/\text{day}$ 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/m^2 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/m^2 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 $30 \pm 9 \text{ mg}/\text{kg}/\text{day}$). The combination also led in the kidney to hyperplasia of the afferent arterioles (at $600 \pm 188 \text{ mg}/\text{kg}/\text{day}$ in rats and from $30 \pm 9 \text{ mg}/\text{kg}/\text{day}$ 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/m^2 basis. These doses in rat, respectively, represent 18 and 73 times the maximum recommended human dose (MRHD) of valsartan and hydrochlorothiazide on a mg/m^2 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 $\text{mg}/\text{kg}/\text{day}$) 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 $\text{mg}/\text{kg}/\text{day}$) are approximately 18 times the maximum recommended human dose on a mg/m^2 basis (calculations assume an oral dose of 320 mg/day and a 60 kg patient). 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

silica, colloidal anhydrous
magnesium stearate/sodium lauryl sulfate
cellulose, microcrystalline
pregelatinised maize starch
lactose monohydrate

crospovidone
povidone
magnesium stearate

Film-coating:

hypromellose
titanium dioxide (E171)
macrogol
talc
vanillin
iron oxide (E172):
80 mg / 12.5 mg: yellow & red iron oxide
160 mg / 12.5 mg: red iron oxide
160 mg / 25 mg: yellow, red & black iron oxide
320 mg / 12.5 mg: red & black iron oxide
320 mg / 25 mg: yellow iron oxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special storage conditions required.

6.5 Nature and contents of container

OPA/Al/PVC-Aluminium blister packs containing 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Viatris Ltd
Damastown Industrial Park
Mulhuddart
Dublin 15
Dublin
Ierland

8. MARKETING AUTHORISATION NUMBER(S)

Valsartan/Hydrochloorthiazide Viatriis 80 mg/12,5 mg, filmomhulde tabletten:	RVG 109818
Valsartan/Hydrochloorthiazide Viatriis 160 mg/12,5 mg, filmomhulde tabletten:	RVG 109819
Valsartan/Hydrochloorthiazide Viatriis 160 mg/25 mg, filmomhulde tabletten:	RVG 109820
Valsartan/Hydrochloorthiazide Viatriis 320 mg/12,5 mg, filmomhulde tabletten:	RVG 112837
Valsartan/Hydrochloorthiazide Viatriis 320 mg/25 mg, filmomhulde tabletten:	RVG 112838

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning:

Valsartan/Hydrochloorthiazide Viatriis 80 mg/12,5 mg, filmomhulde tabletten:	31 juli 2012
Valsartan/Hydrochloorthiazide Viatriis 160 mg/12,5 mg, filmomhulde tabletten:	31 juli 2012
Valsartan/Hydrochloorthiazide Viatriis 160 mg/25 mg, filmomhulde tabletten:	31 juli 2012
Valsartan/Hydrochloorthiazide Viatriis 320 mg/12,5 mg, filmomhulde tabletten:	22 mei 2013
Valsartan/Hydrochloorthiazide Viatriis 320 mg/25 mg, filmomhulde tabletten:	22 mei 2013

Datum van laatste hernieuwing:

Valsartan/Hydrochloorthiazide Viatriis 80/12,5 mg, filmomhulde tabletten:	30 maart 2015
Valsartan/Hydrochloorthiazide Viatriis 160/12,5 mg, filmomhulde tabletten:	30 maart 2015
Valsartan/Hydrochloorthiazide Viatriis 160/25 mg, filmomhulde tabletten:	30 maart 2015
Valsartan/Hydrochloorthiazide Viatriis 320/12,5 mg, filmomhulde tabletten:	30 maart 2015
Valsartan/Hydrochloorthiazide Viatriis 320/25 mg, filmomhulde tabletten:	30 maart 2015

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8: 20 januari 2025.