Tritace Comp 2.5 mg / 12.5 mg
Tritace Comp 5 mg / 25 mg

1. NAME OF THE MEDICINAL PRODUCT

Tritace Comp 2.5 mg/12.5 mg tablets
Tritace Comp 5 mg/25 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tritace Comp 2.5 mg/12.5 mg
Each tablet contains 2.5 mg ramipril and 12.5 mg hydrochlorothiazide

Tritace Comp 5 mg/25 mg
Each tablet contains 5 mg ramipril and 25 mg hydrochlorothiazide

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet 2.5 mg/12.5 mg
White to almost white oblong tablet with score line, both sides embossed with **HNV** and a logo. The tablet can be divided into equal halves.

Tablet 5 mg/25 mg
White to almost white oblong tablet with score line, both sides embossed with **HNW** and a logo. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.

Tritace comp is indicated in patients whose blood pressure cannot be adequately lowered with ramipril alone or hydrochlorothiazide alone.

4.2 Posology and method of administration

Posology

It is recommended that TRITACE COMP is taken once daily, at the same time of the day, usually in the morning.
TRITACE COMP can be taken before, with or after meals, because food intake does not modify its bioavailability (see section 5.2).

TRITACE COMP has to be swallowed with some liquid. The tablet must not be chewed or crushed.

Adults
The dose should be individualised according to the patient profile (see section 4.4) and blood pressure control. The administration of the fixed combination of ramipril and hydrochlorothiazide is usually recommended after dosage titration with one of the individual components.

TRITACE COMP should be started at the lowest possible dosage.
If necessary, the dose can be gradually increased to achieve target blood pressure; the maximum permitted doses are 10 mg of ramipril and 25 mg of hydrochlorothiazide daily.

Special populations

Patients treated with diuretics
Caution should be exercised in patients on diuretics, as hypotension may occur at the start of therapy. Prior to initiating treatment with TRITACE COMP, a dose reduction or discontinuation of the diuretic should be considered.

Should discontinuation not be possible, it is recommended that treatment be initiated with the smallest possible dosage of ramipril (1.25 mg daily) in a free combination. It is recommended that, subsequently, a changeover be made to an initial daily dose of not more than 2.5 mg ramipril/12.5 mg hydrochlorothiazide.

Patients with renal impairment
TRITACE COMP is contraindicated in severe renal impairment due to the hydrochlorothiazide component (creatinine clearance < 30 ml/min) (see section 4.3).
Patients with impairment of renal function may require reduced doses of TRITACE COMP. Patients with creatinine clearance levels between 30 and 60 ml/min should only be treated with the lowest fixed dose combination of ramipril and hydrochlorothiazide after administration of ramipril alone. The maximum permitted doses are 5 mg of ramipril and 25 mg of hydrochlorothiazide daily.

Patients with hepatic impairment
In patients with mild to moderate hepatic impairment, treatment with TRITACE COMP must be initiated only under close medical supervision and the maximum daily doses are 2.5 mg of ramipril and 12.5 mg of hydrochlorothiazide.
TRITACE COMP is contraindicated in severe hepatic impairment (see section 4.3).

Elderly
Initial doses should be lower and subsequent dose titration should be more gradual because of greater chance of undesirable effects especially in very old and frail patients.

Paediatric population
TRITACE COMP is not recommended for use in children and adolescents below 18 years of age due to insufficient data on safety and efficacy.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any other ACE (Angiotensin Converting Enzyme) inhibitor, hydrochlorothiazide, other thiazide diuretics, sulfonamides or any of the excipients listed in section 6.1.
- History of angioedema (hereditary, idiopathic or due to previous angioedema with ACE inhibitors or AIIRAs)
- Concomitant use with sacubitril/valsartan therapy (see sections 4.4 and 4.5).
- Extracorporeal treatments leading to contact of blood with negatively charged surfaces (see section 4.5)
- Significant bilateral renal artery stenosis or renal artery stenosis in a single functioning kidney
- 2nd and 3rd trimester of pregnancy (see sections 4.4 and 4.6)
- Lactation (see section 4.6)
- Severe impairment of renal function with a creatinine clearance below 30 ml/min in undialysed patients
- Clinically relevant electrolyte disturbances which may worsen following treatment with TRITACE COMP (see section 4.4)
- Severe impairment of liver function
- Hepatic encephalopathy
- The concomitant use of TRITACE COMP with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Special populations

- *Pregnancy*: ACE inhibitors such as ramipril, or Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued ACE inhibitor/ 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 ACE inhibitors/ AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

- *Patients at particular risk of hypotension*

- Patients with strongly activated renin-angiotensin-aldosterone system
Patients with strongly activated renin-angiotensin-aldosterone system are at risk of an acute pronounced fall in blood pressure and deterioration of renal function due to ACE inhibition, especially when an ACE inhibitor or a concomitant diuretic is given for the first time or at first dose increase.
Significant activation of renin-angiotensin-aldosterone system is to be anticipated and medical supervision including blood pressure monitoring is necessary, for example in:

- patients with severe hypertension
- patients with decompensated congestive heart failure
- patients with haemodynamically relevant left ventricular inflow or outflow impediment (e.g. stenosis of the aortic or mitral valve)

- patients with unilateral renal artery stenosis with a second functional kidney
- patients in whom fluid or salt depletion exists or may develop (including patients with diuretics)
- patients with liver cirrhosis and/or ascites
- patients undergoing major surgery or during anaesthesia with agents that produce hypotension.

Generally, it is recommended to correct dehydration, hypovolaemia or salt depletion before initiating treatment (in patients with heart failure, however, such corrective action must be carefully weighed out against the risk of volume overload).

- Patients at risk of cardiac or cerebral ischaemia in case of acute hypotension
The initial phase of treatment requires special medical supervision.

- *Primary Hyperaldosteronism*

The combination ramipril + hydrochlorothiazide does not represent a treatment of choice for primary hyperaldosteronism. If ramipril + hydrochlorothiazide is used in a patient with primary hyperaldosteronism, then careful monitoring of plasma potassium level is required.

- *Elderly*

See section 4.2

- *Patients with liver disease*

Electrolyte disturbances due to diuretic therapy including hydrochlorothiazide may cause hepatic encephalopathy in patients with liver disease.

Surgery
It is recommended that treatment with angiotensin converting enzyme inhibitors such as ramipril should be discontinued where possible one day before surgery.

Monitoring of renal function
Renal function should be assessed before and during treatment and dosage adjusted especially in the initial weeks of treatment. Particularly careful monitoring is required in patients with renal impairment (see section 4.2). There is a risk of impairment of renal function, particularly in patients with congestive heart failure or after renal transplant or with renovascular disease including patients with haemodynamically relevant unilateral renal artery stenosis.

Renal impairment
In patients with renal disease, thiazides may precipitate uraemia. Cumulative effects of the active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy (see section 4.3).

Electrolyte imbalance
As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Although hypokalaemia may develop with the use of thiazide

diuretics, concurrent therapy with ramipril may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing rapid diuresis, in patients who are receiving inadequate electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5). The first measurement of plasma potassium levels should be carried out during the first week following the start of treatment. If low potassium levels are detected, correction is required.
Dilutional hyponatraemia may occur. Reduction in sodium levels can be initially asymptomatic and regular testing is therefore essential. Testing should be more frequent in elderly and cirrhotic patients.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Electrolyte Monitoring: Hyperkalaemia
Hyperkalaemia has been observed in some patients treated with ACE inhibitors including TRITACE COMP. Patients at risk for development of hyperkalaemia include those with renal insufficiency, age (> 70 years), uncontrolled diabetes mellitus, or those using potassium salts, potassium retaining diuretics and other plasma potassium increasing active substances or conditions such as dehydration, acute cardiac decompensation, metabolic acidosis. If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

Electrolyte Monitoring: Hyponatremia
Syndrome of Inappropriate Anti-diuretic Hormone (SIADH) and subsequent hyponatremia has been observed in some patients treated with ramipril. It is recommended that serum sodium levels be monitored regularly in the elderly and in other patients at risk of hyponatremia.

Hepatic Encephalopathy
Electrolyte disturbances due to diuretic therapy including hydrochlorothiazide may cause hepatic encephalopathy in patients with liver disease. Treatment should be immediately discontinued in case of hepatic encephalopathy.

Hypercalcaemia
Hydrochlorothiazide stimulates renal calcium reabsorption and may cause hypercalcaemia. It may interfere with test for parathyroid function.

Angioedema
Angioedema has been reported in patients treated with ACE inhibitors including ramipril (see section 4.8). This risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) may be increased in patients taking concomitant medications which may cause angioedema such as mTOR (mammalian target of rapamycin) inhibitors (e.g. temsirolimus, everolimus, sirolimus), vildagliptin or neprilysin (NEP) inhibitors (such as racecadotril). The combination of ramipril with sacubitril/valsartan is contraindicated due to the increased risk of angioedema (see sections 4.3 and 4.5).

In case of angioedema TRITACE COMP must be discontinued. Emergency therapy should be instituted promptly. Patient should be kept under observation for at least 12 to 24 hours and discharged after complete resolution of the symptoms.

Intestinal angioedema has been reported in patients treated with ACE inhibitors including TRITACE COMP (see section 4.8). These patients presented with abdominal pain (with or without nausea or vomiting).
The intestinal angioedema symptoms resolved after stopping the ACE inhibitor.

Anaphylactic reactions during desensitization
The likelihood and severity of anaphylactic and anaphylactoid reactions to insect venom and other allergens are increased under ACE inhibition. A temporary discontinuation of TRITACE COMP should be considered prior to desensitization.

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, Tritace comp should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Neutropenia/agranulocytosis
Neutropenia/agranulocytosis have been rarely seen and bone marrow depression has also been reported. It is recommended to monitor the white blood cell count to permit detection of a possible leucopoenia. More frequent monitoring is advised in the initial phase of treatment and in patients with impaired renal function, those with concomitant collagen disease (e.g. lupus erythematosus or scleroderma), and all those treated with other medicinal products that can cause changes in the blood picture (see sections 4.5 and 4.8).

Choroidal effusion, acute Myopia and Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, can cause 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 treatments 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.

Ethnic differences
ACE inhibitors cause higher rate of angioedema in black patients than in non black patients.
As with other ACE inhibitors, ramipril may be less effective in lowering blood pressure in black people than in non black patients, possibly because of a higher prevalence of hypertension with low renin level in the black hypertensive population.

Athletes
Hydrochlorothiazide may produce a positive analytic result in the anti-doping test.

Metabolic and endocrine effects
Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Hyperuricaemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Cough
Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is non-productive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Other
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

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.

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).

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

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)

Contra-indicated combinations

The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see sections 4.3 and 4.4). Treatment with ramipril must not be started until 36 hours after taking the last dose of sacubitril/valsartan. Sacubitril/valsartan must not be started until 36 hours after the last dose of TRITACE COMP.

Extracorporeal treatments leading to contact of blood with negatively charged surfaces such as dialysis or haemofiltration with certain high-flux membranes (e.g. polyacrylonitril membranes) and low density lipoprotein apheresis with dextran sulphate due to increased risk of severe anaphylactoid reactions (see section 4.3). If such treatment is required, consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agent.

Precautions for use

Potassium salts, heparin, potassium-retaining diuretics and other plasma potassium increasing active substances (including Angiotensin II antagonists, trimethoprim and in fixed dose combination with sulfamethoxazole, tacrolimus, ciclosporin): Hyperkalaemia may occur; therefore close monitoring of serum potassium is required.

Antihypertensive agents (e.g. diuretics) and other substances that may decrease blood pressure (e.g. nitrates, tricyclic antidepressants, anaesthetics, acute alcohol intake, baclofen, alfuzosin, doxazosin, prazosin, tamsulosin, terazosin): Potentiation of the risk of hypotension is to be anticipated (see section 4.2 for diuretics).

Vasopressor sympathomimetics and other substances (epinephrine) that may reduce the antihypertensive effect of ramipril: Blood pressure monitoring is recommended. Furthermore, the effect of the vasopressor sympathomimetics may be attenuated by hydrochlorothiazide.

Allopurinol, immunosuppressants, corticosteroids, procainamide, cytostatics and other substances that may change the blood cell count: Increased likelihood of haematological reactions (see section 4.4).

Lithium salts: Excretion of lithium may be reduced by ACE inhibitors and therefore lithium toxicity may be increased. Lithium levels must be monitored. Concomitant use of

thiazide diuretics may increase the risk of lithium toxicity and enhance the already increased risk of lithium toxicity with ACE inhibitors. The combination of ramipril and hydrochlorothiazide with lithium is therefore not recommended.

Antidiabetic agents including insulin: Hypoglycaemic reactions may occur. Hydrochlorothiazide may attenuate the effect of antidiabetic medicines. Particularly close blood glucose monitoring is therefore recommended in the initial phase of co-administration.

Nonsteroidal anti-inflammatory drugs and acetylsalicylic acid: Reduction of the antihypertensive effect of TRITACE COMP is to be anticipated. Furthermore, concomitant treatment of ACE inhibitors and NSAIDs may lead to an increased risk of worsening of renal function and to an increase in kalaemia.

Oral anticoagulants: Anticoagulant effect may be decreased due to concomitant use of hydrochlorothiazide.

Corticosteroids, ACTH, amphotericin B, carbenoxolone, large amounts of liquorice, laxatives (in case of a prolonged use), and other kaliuretic or plasma potassium decreasing agents: Increased risk of hypokalaemia.

Digitalis preparations, active substances known to prolong the QT interval and antiarrhythmics: Their proarrhythmic toxicity may be increased or their antiarrhythmic effect decreased in the presence of electrolyte disturbances (e.g. hypokalaemia, hypomagnesaemia).

Methyldopa: Haemolysis possible.

Colestyramine or other enterally administered ion exchangers: Reduced absorption of hydrochlorothiazide. Sulphonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Curare-type muscle relaxants: Possible intensification and prolongation of the muscular relaxing effect.

Calcium salts and plasma calcium increasing medicinal products: Rise in serum calcium concentration is to be anticipated in case of concomitant administration of hydrochlorothiazide; therefore close monitoring of serum calcium is required.

Carbamazepine: Risk of hyponatraemia due to additive effect with hydrochlorothiazide.

Iodine containing contrast media: In case of dehydration induced by diuretics including hydrochlorothiazide, there is increased risk of acute renal impairment, in particular when use of important doses of iodine containing contrast media.

Penicillin: Hydrochlorothiazide is excreted in the distal tubulus, and reduces excretion of penicillin.

Quinine: Hydrochlorothiazide reduces quinine excretion.

Heparin: Rise in serum potassium concentration possible.

mTOR inhibitors or vildagliptin: An increased risk of angioedema is possible in patients taking concomitant medications such as mTOR inhibitors (e.g. temsirolimus, everolimus, sirolimus) or vildagliptin. Caution should be used when starting therapy (see section 4.4).

Neprilysin (NEP) inhibitors: An increased risk of angioedema has been reported with concomitant use of ACE inhibitors and NEP inhibitor such as racecadotril (see section 4.4)

Sacubitril/valsartan
The concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema.

4.6 Fertility, pregnancy and lactation

Pregnancy

TRITACE COMP is not recommended during the first trimester of pregnancy (see section 4.4) and contraindicated during the second and third trimesters of pregnancy (see section 4.3).

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. Unless continued ACE inhibitor 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 ACE inhibitors should be stopped immediately, and, if appropriate, alternative therapy should be started.
ACE inhibitor/ Angiotensin II Receptor Antagonist (AIIRA) 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 5.3 'Preclinical safety data'). Should exposure to ACE inhibitor have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Newborns whose mothers have taken ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalaemia (see also sections 4.3 and 4.4).

Hydrochlorothiazide, in cases of prolonged exposure during the third trimester of pregnancy, may cause a foeto-placental ischaemia and risk of growth retardation. Moreover, rare cases of hypoglycaemia and thrombocytopenia in neonates have been reported in case of exposure near term. Hydrochlorothiazide can reduce plasma volume as well as the uteroplacental blood flow.

Breast-feeding

TRITACE COMP is contraindicated during breast-feeding.
Ramipril and hydrochlorothiazide are excreted in breast milk to such an extent that effects on the suckling child are likely if therapeutic doses of ramipril and hydrochlorothiazide are administered to breast-feeding women. Insufficient information is available regarding the use of ramipril during breast-feeding and alternative treatments with better established safety profiles during breast-feeding are preferable, especially

while nursing a newborn or preterm infant. Hydrochlorothiazide is excreted in human milk. Thiazides during breast-feeding by lactating mothers have been associated with a decrease or even suppression of lactation. Hypersensitivity to sulphonamide-derived active substances, hypokalaemia and nuclear icterus might occur. Because of the potential for serious reactions in nursing infants from both active substances, a decision should be made whether to discontinue nursing or to discontinue therapy taking account of the importance of this therapy to the mother.

4.7 Effects on ability to drive and use machines

Some adverse effects (e.g. symptoms of a reduction in blood pressure such as dizziness) may impair the patient's ability to concentrate and react and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. operating a vehicle or machinery).
This can happen especially at the start of treatment, or when changing over from other preparations. After the first dose or subsequent increases in dose it is not advisable to drive or operate machinery for several hours.

4.8 Undesirable effects

Summary of safety profile

The safety profile of ramipril + hydrochlorothiazide includes adverse reactions occurring in the context of hypotension and/or fluid depletion due to increased diuresis. The ramipril active substance may induce persistent dry cough, while the hydrochlorothiazide active substance may lead to worsening of glucose, lipid and uric acid metabolism. The two active substances have inverse effects on plasma potassium. Serious adverse reactions include angioedema or anaphylactic reaction, renal or hepatic impairment, pancreatitis, severe skin reactions and neutropenia/agranulocytosis.

Tabulated list of adverse reactions

Adverse reactions frequency is defined 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, undesirable effects are presented in order of decreasing seriousness.

	Common	Uncommon	Very rare	Not known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				Non-melanoma skin cancer* (Basal cell carcinoma and Squamous cell carcinoma) *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).
Blood and lymphatic system disorders		White blood cell count decreased, red blood cell count decreased, haemoglobin decreased, haemolytic anaemia, platelet count decreased		Bone marrow failure, neutropenia including agranulocytosis, pancytopenia, eosinophilia, haemoconcentration in the context of fluid depletion
Immune system disorders				Anaphylactic or anaphylactoid reactions to either ramipril or anaphylactic reaction to hydrochlorothiazide, antinuclear antibody increased
Endocrine disorders				Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Diabetes mellitus inadequate control, glucose tolerance decreased, blood glucose increased, blood uric acid increased, gout aggravated, blood cholesterol and/or	Anorexia, decreased appetite Blood potassium decreased, thirst due to hydrochlorothiazide	Blood potassium increased due to ramipril	Blood sodium decreased Glycosuria, metabolic alkalosis, hypochloraemia, hypomagnesaemia, hypercalcaemia, dehydration due to hydrochlorothiazide

	triglycerides increased due to hydrochlorothiazide			
Psychiatric disorders		Depressed mood, apathy, anxiety, nervousness, sleep disorders including somnolence		Confusional state, restlessness, disturbance in attention
Nervous system disorders	Headache, dizziness	Vertigo, paraesthesia, tremor, balance disorder, burning sensation, dysgeusia, ageusia		Cerebral ischaemia including ischaemic stroke and transient ischaemic attack, psychomotor skills impaired, parosmia
Eye disorders		Visual disturbance including blurred vision, conjunctivitis		Xanthopsia, lacrimation decreased due to hydrochlorothiazide; choroidal effusion, secondary acute angle- closure glaucoma and/or acute myopia due to hydrochlorothiazide
Ear and labyrinth disorders		Tinnitus		Hearing impaired
Cardiac disorders		Myocardial ischaemia including angina pectoris, tachycardia, arrhythmia, palpitations, oedema peripheral		Myocardial infarction
Vascular disorders		Hypotension, orthostatic blood pressure decreased,		Thrombosis in the context of severe fluid depletion, vascular stenosis, hypoperfusion,

		syncope, flushing		Raynaud's phenomenon, vasculitis
Respiratory, thoracic and mediastinal disorders	Non-productive tickling cough, bronchitis	Sinusitis, dyspnoea, nasal congestion	Acute respiratory distress syndrome (ARDS) (see section 4.4)	Bronchospasm including asthma aggravated Alveolitis allergic, non cardiogenic pulmonary oedema due to hydrochlorothiazide
Gastrointestinal disorders		Gastrointestinal inflammation, digestive disturbances, abdominal discomfort, dyspepsia, gastritis, nausea, constipation Gingivitis due to hydrochlorothiazide	Vomiting, aphtous stomatitis, glossitis, diarrhoea, abdominal pain upper, dry mouth	Pancreatitis (cases of fatal outcome have been very exceptionally reported with ACE inhibitors), pancreatic enzymes increased, small bowel angioedema Sialoadenitis due to hydrochlorothiazide
Hepatobiliary disorders		Cholestatic or cytolytic hepatitis (fatal outcome has been very exceptional), hepatic enzyme and/or bilirubin conjugated increased Calculous cholecystitis due to hydrochlorothiazide		Acute hepatic failure, jaundice cholestatic, hepatocellular damage
Skin and subcutaneous tissue disorders		Angioedema: very exceptionally, the airway obstruction resulting from		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme,

		angioedema may have a fatal outcome; dermatitis psoriasiform, hyperhidrosis, rash, in particular maculo-papular, pruritus, alopecia		pemphigus, psoriasis aggravated, exfoliative dermatitis, photosensitivity reaction, onycholysis, pemphigoid or lichenoid exanthema or enanthema, urticaria Systemic lupus erythematosus due to hydrochlorothiazide
Musculoskeletal and connective tissue disorders		Myalgia		Arthralgia, muscle spasms Muscular weakness, musculoskeletal stiffness, tetany due to hydrochlorothiazide
Renal and urinary disorders		Renal impairment including renal failure acute, urine output increased, blood urea increased, blood creatinine increased		Worsening of a pre-existing proteinuria Interstitial nephritis due to hydrochlorothiazide
Reproductive system and breast disorders		Transient erectile impotence		Libido decreased, gynaecomastia
General disorders and administration site conditions	Fatigue, asthenia	Chest pain, pyrexia		

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms

Symptoms associated with overdosage of ACE inhibitors may include excessive peripheral vasodilatation (with marked hypotension, shock), bradycardia, electrolyte disturbances, renal failure, cardiac arrhythmia, impairment of consciousness including coma, cerebral convulsions, pareses, and paralytic ileus.
In predisposed patients (e.g. prostatic hyperplasia) hydrochlorothiazide overdose may induce acute urinary retention.

Management

The patient should be closely monitored and the treatment should be symptomatic and supportive. Suggested measures include primary detoxification (gastric lavage, administration of adsorbents) and measures to restore haemodynamic stability, including administration of alpha 1 adrenergic agonists or angiotensin II (angiotensinamide) administration. Ramiprilat, the active metabolite of ramipril is poorly removed from the general circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ACE inhibitors and diuretics, ramipril and diuretics, ATC code C09BA05

Mechanism of action

Ramipril
Ramiprilat, the active metabolite of the prodrug ramipril, inhibits the enzyme dipeptidylcarboxypeptidase I (synonyms: angiotensin-converting enzyme; kininase II). In plasma and tissue, this enzyme catalyses the conversion of angiotensin I to the active vasoconstrictor substance angiotensin II, as well as the breakdown of the active vasodilator bradykinin. Reduced angiotensin II formation and inhibition of bradykinin breakdown lead to vasodilatation.

Since angiotensin II also stimulates the release of aldosterone, ramiprilat causes a reduction in aldosterone secretion. The average response to ACE inhibitor monotherapy was lower in black (Afro-Caribbean) hypertensive patients (usually a low-renin hypertensive population) than in non-black patients.

Hydrochlorothiazide
Hydrochlorothiazide is a thiazide diuretic. The mechanism of antihypertensive effect of thiazide diuretics is not fully known. It inhibits the reabsorption of sodium and chloride in the distal tubule. The increased renal excretion of these ions is accompanied by increased urine output (due to osmotic binding of water). Potassium and magnesium excretion are increased, uric acid excretion is decreased. Possible mechanisms of the antihypertensive action of hydrochlorothiazide could be: the modified sodium balance, the reduction in extracellular water and plasma volume, a change in renal vascular resistance as well as a reduced response to norepinephrine and angiotensin II.

Pharmacodynamic effects
Ramipril
Administration of ramipril causes a marked reduction in peripheral arterial resistance. Generally, there are no major changes in renal plasma flow and glomerular filtration rate. Administration of ramipril to patients with hypertension leads to a reduction in supine and standing blood pressure without a compensatory rise in heart rate.
In most patients the onset of the antihypertensive effect of a single dose becomes apparent 1 to 2 hours after oral administration. The peak effect of a single dose is usually reached 3 to 6 hours after oral administration. The antihypertensive effect of a single dose usually lasts for 24 hours.
The maximum antihypertensive effect of continued treatment with ramipril is generally apparent after 3 to 4 weeks. It has been shown that the antihypertensive effect is sustained under long term therapy lasting 2 years.
Abrupt discontinuation of ramipril does not produce a rapid and excessive rebound increase in blood pressure.

Hydrochlorothiazide
With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6 to 12 hours.
The onset of the antihypertensive effect occurs after 3 to 4 days and can last up to one week after discontinuation of therapy.
The blood-pressure-lowering effect is accompanied by slight increases in the filtration fraction, renal vascular resistance and plasma renin activity.

Clinical efficacy and safety

Concomitant administration of ramipril-hydrochlorothiazide
In clinical trials, the combination led to greater reductions in blood pressure than when either of the products was administered alone. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of ramipril to hydrochlorothiazide tends to reverse the potassium loss associated with these diuretics. Combination of an ACE-inhibitor with a thiazide diuretic produces a synergistic effect and also lessens the risk of hypokalaemia provoked by the diuretic alone.

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.

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 (≥ 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 (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Ramipril

Absorption
Following oral administration ramipril is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations of ramipril are reached within one hour. Based on urinary recovery, the extent of absorption is at least 56 % and is not significantly influenced by the presence of food in the gastrointestinal tract. The bioavailability of the active metabolite ramiprilat after oral administration of 2.5 mg and 5 mg ramipril is 45 %. Peak plasma concentrations of ramiprilat, the sole active metabolite of ramipril are reached 2-4 hours after ramipril intake. Steady-state plasma concentrations of ramiprilat after once daily dosing with the usual doses of ramipril are reached by about the fourth day of treatment.

Distribution
The serum protein binding of ramipril is about 73 % and that of ramiprilat about 56 %.

Biotransformation
Ramipril is almost completely metabolised to ramiprilat, and to the diketopiperazine ester, the diketopiperazine acid, and the glucuronides of ramipril and ramiprilat.

Elimination
Excretion of the metabolites is primarily renal. Plasma concentrations of ramiprilat decline in a polyphasic manner. Because of its potent, saturable binding to ACE and slow dissociation from the enzyme, ramiprilat shows a prolonged terminal elimination phase at very low plasma concentrations. After multiple once-daily doses of ramipril, the effective half-life of ramiprilat concentrations was 13-17 hours for the 5-10 mg doses and longer for the lower 1.25-2.5 mg doses. This difference is related to the saturable capacity of the enzyme to bind ramiprilat. A single oral dose of ramipril produced an undetectable level of ramipril and its metabolites in breast milk. However, the effect of multiple doses is not known.

Patients with renal impairment (see section 4.2).
Renal excretion of ramiprilat is reduced in patients with impaired renal function, and renal ramiprilat clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of ramiprilat, which decrease more slowly than in subjects with normal renal function.

Patients with liver impairment (see section 4.2).
In patients with impaired liver function, the metabolism of ramipril to ramiprilat was delayed due to diminished activity of hepatic esterases, and plasma ramipril levels in these patients were increased. Peak concentrations of ramiprilat in these patients, however, are not different from those seen in subjects with normal hepatic function.

Hydrochlorothiazide

Absorption
Following oral administration about 70 % of hydrochlorothiazide is absorbed from the gastrointestinal tract. Peak plasma concentrations of hydrochlorothiazide are reached within 1.5 to 5 hours.

Distribution
The plasma protein binding of hydrochlorothiazide is 40 %.

Biotransformation
Hydrochlorothiazide undergoes negligible hepatic metabolism.

Elimination
Hydrochlorothiazide is eliminated almost completely (> 95 %) in an unchanged form through the kidneys; 50 to 70 % of a single oral dose is eliminated within 24 hours. The elimination half-life is 5 to 6 hours.

Patients with renal impairment (see section 4.2)
Renal excretion of hydrochlorothiazide is reduced in patients with impaired renal function, and renal hydrochlorothiazide clearance is proportionally related to creatinine clearance. This results in elevated plasma concentrations of hydrochlorothiazide, which decrease more slowly than in subjects with normal renal function.

Patients with liver impairment (see section 4.2)
In patients with hepatic cirrhosis the pharmacokinetics of hydrochlorothiazide has not changed significantly. The pharmacokinetics of hydrochlorothiazide has not been studied in patients with cardiac failure.

Ramipril and Hydrochlorothiazide
The concurrent administration of ramipril and hydrochlorothiazide does not affect their bioavailability. The combination product can be considered as bioequivalent to products containing the individual components.

5.3 Preclinical safety data

Ramipril + Hydrochlorothiazide
In rats and mice the combination of ramipril and hydrochlorothiazide has no acute toxic activity up to 10,000 mg/kg. Repeated doses administration studies performed in rats and monkeys revealed only disturbances in electrolytes balance.
Reproduction studies in rats and rabbits revealed that the combination is somewhat more toxic than either of the single components but none of the studies revealed a teratogenic effect of the combination.
No studies on mutagenicity and carcinogenicity have been performed with the combination.

Ramipril
Extensive mutagenicity testing using several test systems has yielded no indication that ramipril possesses mutagenic or genotoxic properties.
Long-term studies in rat and mouse have yielded no indication of any tumorigenic effect.
Renal tubules with oxyphilic cells and tubules with oxyphilic cellular hyperplasia in rats are regarded as response to functional alterations and morphological changes, and not as a neoplastic or pre-neoplastic response.

Hydrochlorothiazide
Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 µg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.
Two-year feeding studies in mice and rats conducted under the auspices of the US National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized starch, microcrystalline cellulose, hydroxypropylmethylcellulose and sodium stearyl fumarate.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

2.5 mg/12.5 mg: packs of 14, 28 tablets in PVC/Alu blisters
5 mg/25 mg: packs of 14, 28 tablets in PVC/Alu blisters
Not all pack sizes may be marketed.

8. MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi Israel Ltd, Greenwork Complex, P.O box 47,Yakum

Revised in October 2023 according to MOH's guidelines.