

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CoLosar-Denk 100/12.5

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances: losartan and hydrochlorothiazide

Each film-coated tablet contains 100 mg losartan potassium equivalent to 91.52 mg losartan and 12.5 mg hydrochlorothiazide (HCT).

Excipient with known effect: Each film-coated tablet contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, round, biconvex, film-coated tablet, scored on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CoLosar-Denk 100/12.5 is indicated for the treatment of essential hypertension in patients whose blood pressure cannot be adequately controlled on losartan or hydrochlorothiazide alone.

4.2 Posology and method of administration

Posology

Hypertension

Losartan/HCT is not suitable for use as initial treatment, but for the treatment of patients whose blood pressure is not adequately controlled on losartan potassium or hydrochlorothiazide alone.

Dosage titration with the individual components (losartan and hydrochlorothiazide) is recommended.

Where clinically appropriate, a direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.

The usual maintenance dose is one tablet of 50 mg losartan potassium and 12.5 mg HCT once daily. Tablets of this strength are also available. For patients who do not respond adequately, this dose may be increased to 1 tablet of CoLosar-Denk 100/12.5 (100 mg losartan potassium and 12.5 mg HCT) once daily.

In general, the blood pressure lowering effect is attained within three to four weeks after the commencement of therapy. CoLosar-Denk 100/12.5 (100 mg losartan potassium and 12.5 mg HCT) is

suitable for patients already treated with losartan 100 mg and who need an additional control of blood pressure.

Use in patients with renal impairment and haemodialysis patients

No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance of 30-50 ml/min). Losartan/HCT tablets are not recommended for patients receiving haemodialysis. Losartan/HCT tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance < 30 ml/min) (see section 4.3).

Use in patients with intravascular volume depletion

Volume depletion and/or sodium loss should be corrected before administering losartan/HCT tablets.

Use in patients with hepatic impairment

Losartan/HCT is contraindicated in patients with severe liver impairment (see section 4.3).

Use in elderly patients

Dosage adjustment is not generally necessary for elderly patients.

Paediatric population (under 18 years of age)

There is no experience in children and adolescents. Therefore, losartan/HCT tablets should not be administered to children or adolescents.

Method of administration

This medicine may be administered with other antihypertensives (see sections 4.3, 4.4, 4.5 and 5.1).

The tablets should be swallowed with a glass of water.

The tablets may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to the active substances, sulphonamide derivatives or to any of the excipients listed in section 6.1,
- refractory hypokalaemia or hypercalcaemia,
- severe hepatic impairment, cholestasis and biliary obstructive disorders,
- refractory hyponatraemia,
- symptomatic hyperuricaemia/gout,
- pregnancy and lactation,
- severe renal impairment (creatinine clearance < 30 ml/min),
- anuria,
- The concomitant use of losartan/HCT 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

Losartan

Angiooedema

Patients with a history of angiooedema (swelling of the face, lips, throat and/or tongue) should be closely monitored (see section 4.8.).

Hypotension and intravascular volume depletion

Symptomatic hypotension, especially after the first dose or after an increase in dosage, may occur in patients who are volume- and/or sodium-depleted by forced diuresis or high doses of diuretics, low salt diet, diarrhoea or vomiting. Such conditions should be corrected before administering losartan/HCT tablets (see sections 4.2 and 4.3).

Electrolyte imbalance

Electrolyte imbalance is common in patients with renal impairment, with or without diabetes, and should be corrected. Therefore, serum potassium levels and creatinine clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium sparing diuretics, potassium supplements, potassium containing salt substitutes or other substances that may increase serum potassium levels (e.g. trimethoprim) in combination with losartan is not recommended (see section 4.5).

Impaired liver function

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in patients with liver cirrhosis, losartan/HCT should be administered with caution in patients with a history of mild to moderate liver impairment. There is no therapeutic experience with losartan in patients with severe liver impairment. Losartan/HCT is therefore contraindicated in patients with severe liver impairment (see sections 4.2, 4.3 and 5.2).

Impaired renal function

As a consequence of inhibiting the renin-angiotensin system, changes in renal function, including renal failure, have been reported (particularly in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As applies to other drugs that interfere with the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have been observed in patients with bilateral renal arterial stenosis or with single renal arterial stenosis in patients with only one kidney. Such changes in renal function may be reversible upon discontinuation of treatment. Losartan should be used with caution in patients with bilateral renal arterial stenosis or with single renal arterial stenosis in patients with only one kidney.

Kidney transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism generally will not respond to antihypertensive agents that act by inhibiting the renin-angiotensin system. Therefore, the use of losartan/HCT is not recommended.

Coronary heart disease and cerebrovascular disease

As applies to all antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure

As with other drugs that act on the renin-angiotensin system, there is a risk of severe arterial hypotension and (often acute) renal impairment in patients suffering from heart failure, with or without renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As applies to other vasodilators, special caution is indicated in patients with aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy.

Ethnic differences

As observed with ACE inhibitors, losartan and other angiotensin II receptor antagonists appear to be less effective in lowering blood pressure in black people than in non-blacks.

This may be due to a higher prevalence of low-renin states among the black hypertensive population.

Pregnancy

Treatment with AIIRAs (Angiotensin II Receptor Antagonists) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to an alternative antihypertensive treatment with an established safety profile for use in pregnant women. If pregnancy is diagnosed, treatment with AIIRAs should be discontinued immediately and, if necessary, alternative treatment should be commenced (see sections 4.3 and 4.6).

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.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of volume or electrolyte depletion, such as fluid loss, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia which may occur in patients suffering from additional diarrhoea or vomiting. Periodic determination of serum electrolytes should be carried out at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may interfere with glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be necessary (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism.

Thiazides should be discontinued before carrying out parathyroid function tests.

Diuretic treatment with thiazides may cause an increase in cholesterol and triglyceride levels.

Thiazide therapy may precipitate hyperuricaemia and/or gout in some patients. As losartan reduces uric acid content, losartan in combination with hydrochlorothiazide may attenuate the diuretic-induced hyperuricaemia.

Impaired liver function

Thiazides should be administered with caution in patients with impaired hepatic function or progressive liver disease, as they may cause intrahepatic cholestasis, and since even minor changes in the fluid and electrolyte balance may precipitate hepatic coma. Losartan/HCT is contraindicated in patients with severe liver impairment (see sections 4.3 and 5.2).

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 (HCT) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCT could act as a possible mechanism for NMSC.

Patients taking HCT 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 HCT may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other

Hypersensitivity reactions may occur in patients receiving thiazides, regardless of whether or not they have a history of allergies or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

The use of losartan/hydrochlorothiazide can produce positive results in anti-doping tests.

This medicine contains lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Losartan

Rifampicin and fluconazole have been reported to reduce plasma levels of the active metabolite. The clinical significance of this effect has not been established.

As applies to other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements or of salt substitutes containing potassium may cause an increase in the potassium levels in the blood. Co-medication is not advisable.

As with other drugs that affect sodium excretion, lithium excretion may be reduced. Serum lithium level should therefore be monitored carefully during concomitant administration of lithium salts and angiotensin II receptor antagonists.

When angiotensin II receptor antagonists are co-administered with non-steroidal anti-inflammatory drugs (NSAIDs, i.e. COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs) attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II receptor antagonists and NSAIDs may increase the risk of further impairment of renal function, including possible acute renal failure and an increase in serum potassium, particularly in patients with pre-existing renal function impairment.

These combinations should be used with caution, especially in elderly patients.

Patients should be adequately hydrated and monitoring of renal function should be considered after initiation of combination therapy, and periodically thereafter.

Concomitant use of angiotensin II receptor antagonists and NSAIDs, including selective cyclooxygenase 2 inhibitors, may cause further impairment of renal function in patients with pre-existing renal function impairment. The changes in renal function may be reversible upon discontinuation of treatment.

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).

Other substances which induce hypotension such as tricyclic antidepressants, antipsychotic agents, baclofen, amifostin: Simultaneous use with these drugs that lower blood pressure as a main or side effect may increase the risk of hypotension.

Hydrochlorothiazide

When given concurrently, the following medicines may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants:
Potentiation of orthostatic hypotension may occur.

Antidiabetics (oral agents and insulin):
Treatment with thiazides may interfere with glucose tolerance. Dosage adjustment of the antidiabetic agent may be required. Metformin should be used with caution due to the risk of lactic acidosis caused by possible restriction of renal function linked to HCT.

Other antihypertensive agents:
Additive effect.

Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 % and 43 %, respectively.

Corticosteroids, ACTH:
Intensified electrolyte depletion, particularly hypokalaemia.

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

Non-depolarising muscle relaxants (e.g. tubocurarine):
Possible increased responsiveness to muscle relaxants.

Lithium:
Diuretic drugs reduce renal clearance of lithium and therefore significantly increase the risk of lithium toxicity. Concomitant administration is not recommended.

Medicines to treat gout (probenecid, sulfinpyrazone and allopurinol):
Dosage adjustment of uricosuric medicines may be necessary as hydrochlorothiazide may raise serum uric acid levels. It may be necessary to increase the dose of probenecid or sulfinpyrazone. Co-administration of thiazides may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden):
Reduced gastrointestinal motility and gastric emptying rate increases the bioavailability of thiazide diuretics.

Cytostatic agents (e.g. cyclophosphamide, methotrexate):
Thiazides may reduce the renal excretion of cytostatic agents and thus potentiate their myelosuppressive effects.

Salicylates:
In case of high doses of salicylates, hydrochlorothiazide may enhance the toxic effect of salicylates on the central nervous system.

Methyldopa:

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Ciclosporine:

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

Digitalis glycosides:

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Pharmaceutical products affected by serum potassium fluctuations:

Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is administered with pharmaceutical products affected by serum potassium fluctuations (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing pharmaceutical products (including some antiarrhythmics), hypokalaemia being a predisposing factor for torsades de pointes (ventricular tachycardia):

- 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 as IV application, halofantrin, mizolastin, pentamidine, terfenadine, vincamine as IV application).

Calcium salts:

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Pharmaceutical products/laboratory test interactions:

Because of their effects on calcium metabolism, thiazides may interfere with parathyroid function tests (see section 4.4).

Carbamazepine:

Risk of symptomatic hyponatraemia. Clinical and biological monitoring is required.

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 containing product.

Patients should be rehydrated before use.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives or glycyrrhizin (found in liquorice):

Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnancy

Losartan/hydrochlorothiazide is contraindicated during pregnancy.

Angiotensin II receptor antagonists (AIIRAs):

Epidemiological data relating to teratogenic risk associated with the use of ACE inhibitors during the first trimester of pregnancy have not been conclusive. However, a slight increase in risk cannot be excluded. As long as there are no controlled epidemiological data relating to the risk of angiotensin II receptor antagonists, similar risks for this class of drug cannot be ruled out. Patients who are planning a pregnancy should be changed over to alternative antihypertensive agents which have an established safety profile for use during pregnancy. If pregnancy is diagnosed, losartan should be discontinued immediately and, if indicated, an alternative treatment should be commenced.

Exposure to losartan during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3). Should exposure to losartan have occurred during the final 6 months of pregnancy, ultrasound examination of renal function and skull is recommended.

Neonates whose mothers have taken losartan during pregnancy should be closely monitored for hypotension (see also sections 4.3 and 4.4).

Hydrochlorothiazide:

There is only limited experience on the use of hydrochlorothiazide during pregnancy, especially during the first trimester. Findings from animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Because of the pharmacological action of hydrochlorothiazide, its use during the second and third trimester may disrupt foetal placental perfusion and may cause foetal and neonatal effects like icterus, electrolyte imbalance and thrombocytopenia. Hydrochlorothiazide should not be used in the presence of gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should be used in pregnant women with hypertension only in the rare cases in which no other therapy is possible.

Breast-feeding

Angiotensin II receptor antagonists (AIIRAs):

As there is no information available on the use of the combination losartan and hydrochlorothiazide during breast feeding, this is not recommended and other treatment options which have established safety profiles during breast-feedingshould be favoured in particular when breast-feeding infants or preterm infants.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of losartan/hydrochlorothiazide during breast-feeding is not recommended. If losartan/hydrochlorothiazide is used during breast-feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and operate machinery have been conducted. However, when driving a vehicle or operating machines it should be taken into account that dizziness or tiredness may occasionally occur when taking antihypertensive medications, especially at the beginning of treatment or when a dose is increased.

4.8 Undesirable effects

The adverse reactions below are classified where appropriate by system organ class and frequency according to 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 assessed on the basis of the available data).

In clinical studies with losartan potassium and hydrochlorothiazide, no adverse drug reactions peculiar to this drug combination were observed. The adverse drug reactions that occurred were restricted to those which were formerly observed with losartan potassium and/or hydrochlorothiazide.

In controlled clinical studies for essential hypertension, dizziness was the only adverse drug reaction reported that occurred with an incidence of 1 % or more in the losartan/HCT group more frequently than in the placebo group.

In addition to these effects, the following further adverse drug reactions were reported after the introduction of the product to the market:

System organ class	Adverse reaction	Frequency
Hepato-biliary disorders	Hepatitis	Rare
Investigations	Hyperkalaemia, elevation of ALT	Rare

The following additional adverse drug reactions have been seen with one of the individual components and may be potential adverse drug reactions with losartan/hydrochlorothiazide:

Losartan

The following adverse reactions have been reported for losartan in clinical studies and in post-marketing experience:

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis	Uncommon
	Thrombocytopenia	Not known
Cardiac disorders	Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II AV block, cerebrovascular accident, myocardial infarction, palpitations, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)	Uncommon
Ear and labyrinth disorders	Vertigo, tinnitus	Uncommon
Eye disorders	Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity	Uncommon
Gastrointestinal disorders	Abdominal pain, nausea, diarrhoea, dyspepsia	Common
	Constipation, tooth ache, dry mouth, flatulence, gastritis, vomiting, obstipation	Uncommon
	Pancreatitis	Not known
General disorders and administration site conditions	Asthenia, fatigue, chest pain	Common
	Facial oedema, oedema, fever	Uncommon
	flu-like symptoms, malaise	Not known
Hepatobiliary disorders	Liver function abnormalities	Not known
Immune system disorders	Hypersensitivity, anaphylactic reactions, angioedema including swelling of the larynx	Rare

System organ class	Adverse reaction	Frequency
	and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors	
Metabolism and nutrition disorders	Anorexia, gout	Uncommon
Musculoskeletal and connective tissue disorders	Muscle cramp, back pain, leg pain, myalgia	Common
	Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness	Uncommon
	Rhabdomyolysis	Not known
Nervous system disorders	Headache, dizziness	Common
	Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope	Uncommon
	Dysgeusia	Not known
Psychiatric disorders	Insomnia	Common
	Anxiety, anxiety/panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment	Uncommon
Renal and urinary disorders	Renal impairment, renal failure	Common
	Nocturia, frequent urination, urinary tract infections	Uncommon
Reproductive system and breast disorders	Decreased libido, erectile dysfunction/impotence	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough, upper respiratory tract infection, nasal congestion, sinusitis, sinus disorder	Common
	Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion	Uncommon
Skin and subcutaneous tissue disorders	Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritis, rash, urticaria, sweating	Uncommon
Vascular disorders	Vasculitis	Uncommon
	Dose-related orthostatic effects	Not known
Investigations	Hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia	Common
	Slight increase in urea and creatinine serum levels	Uncommon
	Increase in hepatic enzymes and bilirubin	Very rare
	Hyponatraemia	Not known

Hydrochlorothiazide

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Agranulocytosis, aplastic anaemia, immune haemolytic anaemia, leukocytopenia, purpura, thrombocytopenia	Uncommon
Immune system disorders	Anaphylactic reactions	Rare

System organ class	Adverse reaction	Frequency
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia	Uncommon
Psychiatric disorders	Insomnia	Uncommon
Nervous system disorders	Headache	Common
Eye disorders	Transient blurred vision, xanthopsia	Uncommon
Vascular disorders	Necrotising angiitis (vasculitis, cutaneous vasculitis)	Uncommon
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis and pulmonary oedema	Uncommon
Gastrointestinal disorders	Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation	Uncommon
Hepatobiliary disorders	Icterus (intrahepatic cholestasis), pancreatitis	Uncommon
Skin and subcutaneous tissue disorders	Photosensitivity, urticaria, toxic epidermal necrolysis	Uncommon
	Cutaneous lupus erythematoses	Not known
Musculoskeletal and connective tissue disorders	Muscle cramps	Uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	Not known
Renal and urinary disorders	Glycosuria, interstitial nephritis, renal dysfunction, renal failure	Uncommon
General disorders and administration site conditions	Fever, dizziness	Uncommon

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCT 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.

4.9 Overdose

No specific information is available on the treatment of overdose with the combination of losartan and HCT. Treatment is symptomatic and supportive. Therapy with losartan/HCT should be discontinued and the patient monitored closely. Suggested measures include induction of emesis if ingestion is recent and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures.

Losartan

Limited data are available in regard to overdose in humans to date. Probable symptoms are hypotension and tachycardia; bradycardia could occur from parasympathic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be initiated.

Neither losartan nor its active metabolite can be removed by haemodialysis.

Hydrochlorothiazide

The most common signs and symptoms are those caused by electrolyte depletion (hypokalaemia, hypochloridaemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established to date.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II receptor blockers (ARBs) and diuretics
ATC Code: C09DA01

Losartan/hydrochlorothiazide (HCT)

The components of losartan/HCT have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect appears to be the result of the complementary actions of both components. As a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity and aldosterone secretion as well as the angiotensin II level whereas it decreases serum potassium. Losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could have a tendency to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a transient and mild uricosuric effect. Hydrochlorothiazide causes moderate increases in uric acid. The combination of losartan and hydrochlorothiazide tends to attenuate the diuretic-induced hyperuricaemia.

The antihypertensive effect of losartan/HCT is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of losartan/HCT had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with 50 mg losartan potassium/12.5 mg hydrochlorothiazide, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

Losartan/HCT is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (< 65 years) and older (\geq 65 years) patients and is effective in all degrees of hypertension.

Losartan

Losartan is a synthetically produced oral angiotensin II receptor (type AT₁) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin-angiotensin system and an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT₁ receptor present in many tissues (i.e. smooth vascular muscle, adrenal gland, kidneys and heart) and elicits some important biological effects, such as vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT₁ receptor. Losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant effects of angiotensin II *in vitro* and *in vivo*, regardless of the source or route of its synthesis. Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels which play an important part in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no increase in bradykinin-related adverse drug reactions.

The removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA) during administration of losartan. An increase in PRA causes an increase in angiotensin II in plasma. Despite these increases, antihypertensive effect and suppression of plasma aldosterone

concentration are maintained, indicating effective angiotensin II receptor blockade. After the discontinuation of losartan, PRA and angiotensin II levels fell within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT₁ receptor than for the AT₂ receptor. The active metabolite is 10 to 40 times more effective than losartan on a weight basis.

In a study designed to assess the incidence of cough in patients receiving losartan as compared to patients being treated with ACE inhibitors, the incidence of cough reported by patients receiving losartan or hydrochlorothiazide was similar and was significantly less than in patients receiving an ACE inhibitor. In addition, in an overall analysis of 16 double-blind clinical studies involving 4131 patients, the incidence of spontaneously reported cough in patients receiving losartan (3.1 %) was similar to that of patients treated with placebo (2.6 %) or hydrochlorothiazide (4.1 %) whereas the incidence with ACE inhibitors was 8.8 %.

Administration of losartan potassium significantly reduced proteinuria and fractional excretion of albumin and IgG in non-diabetic hypertensive patients with proteinuria. Losartan maintains glomerular filtration rate and reduces filtration fraction. Losartan persistently reduces serum uric acid (usually <0.4 mg/dl) during long-term therapy as well.

Losartan has no effect on autonomic reflexes and has no sustained effect on plasma noradrenaline.

In patients with left ventricular heart failure, 25 mg and 50 mg of losartan produced positive haemodynamic and neurohormonal effects. These were characterised by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate as well as a reduction in aldosterone and norepinephrine levels in the blood. The occurrence of hypotension was dose-related in these heart failure patients.

Hypertension studies

In controlled clinical studies, once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose as opposed to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. The blood pressure reduction at the end of the dosing interval was about 70-80 % of the effect seen 5-6 hours after administration.

Discontinuation of losartan in hypertensive patients did not cause an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, losartan did not have a clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

LIFE study

The study Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) was a randomised, triple-blind, active-controlled study with 9193 hypertensive patients aged between 55 and 80 years with left ventricular hypertrophy by ECG criteria.

The patients were randomly assigned to receive either 50 mg losartan or 50 mg atenolol once a day. If the target blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was administered in addition and, if necessary, the dose of losartan or atenolol was then increased to 100 mg once a day. Where required, other antihypertensive agents, with the exception of ACE inhibitors, angiotensin II receptor antagonists and beta receptor blockers, were given in addition in both groups in order to achieve a similar hypotensive effect in both groups.

The mean period of observation was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly reduced to similar levels in both treatment groups. Treatment with losartan resulted in a 13.0 % risk reduction ($p=0.021$, 95 % confidence interval 0.77-0.98) compared to atenolol with relation to the primary composite endpoint. This was primarily attributable to the reduced incidence of stroke. Treatment with losartan reduced the relative risk of stroke by 25 % ($p=0.001$, 95 % confidence interval 0.63-0.89) compared to atenolol. The incidences of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

ONTARGET and VA NEPHRON-D study

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 study

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

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive action of thiazide diuretics is not fully known. Thiazides interfere with electrolyte reabsorption in the renal tubule and directly increase the excretion of sodium and chloride in approximately equivalent amounts. The diuretic effect of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and aldosterone secretion, with consequent increases in urinary potassium and bicarbonate excretion, and a reduction of serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore co-administration of an angiotensin II receptor antagonist and a thiazide tends to reverse the potassium loss associated with thiazide diuretics.

Diuresis occurs within 2 hours of oral administration and the maximum diuretic effect is attained after 4 hours. The duration of action is 6-12 hours and the antihypertensive effect is sustained for up to 24 hours.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between HCT 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 HCT 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 HCT: 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

Absorption

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism. An active carboxylic acid metabolite and further inactive metabolites are formed. The systemic bioavailability of losartan film-coated tablets is approx. 33 %. Mean peak plasma concentrations of losartan and its active metabolite are reached in one hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the medicine was administered with a standardised meal.

Distribution

Losartan

Losartan and its active metabolite are ≥ 99 % bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres. Studies in rats indicate that losartan crosses the blood-brain barrier poorly, if at all.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and passes into breast milk.

Biotransformation

Losartan

About 14 % of an intravenously or orally administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ¹⁴C-labelled losartan, plasma radioactivity is primarily attributable to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of subjects studied.

In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, a N-2 tetrazole glucuronide.

Elimination

Losartan

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively, with renal clearance of about 74 ml/min (losartan) and 26 ml/min (active metabolite). When losartan is administered orally, about 4 % of the dose is excreted unchanged in urine and about 6 % is excreted in urine as active metabolite. The pharmacokinetics of losartan and its active metabolite are linear at oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline poly-exponentially with a terminal half life of about 2 hours and 6-9 hours, respectively. Neither losartan nor its active metabolite accumulates significantly in plasma during once-daily dosing with 100 mg.

Losartan and its metabolites are excreted in bile and urine. Following an oral dose of ¹⁴C-labelled losartan in man, about 35 % of radioactivity is recovered in urine and 58 % in faeces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised but is eliminated rapidly via the kidneys. When plasma levels have been measured for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 % of the oral dose is eliminated unchanged within 24 hours.

Special populations

Losartan / hydrochlorothiazide

Plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives were not significantly different from those in young hypertensives.

Losartan

Following oral administration in patients with mild to moderate alcoholic liver cirrhosis, plasma concentrations of losartan and its active metabolite were, respectively, 5 times and about 1.7 times greater than those seen in young male subjects.

Pharmacokinetic studies showed that the AUC of losartan in Japanese and non-Japanese healthy male subjects is not different. However, the AUC of the carboxylic acid metabolite (E-3174) appears to be different between the two groups, with an approximately 1.5 fold higher exposure in Japanese subjects than in non-Japanese subjects. The clinical significance of these results is not known.

Neither losartan nor its active metabolite can be removed by haemodialysis.

5.3 Preclinical safety data

Preclinical studies, including conventional studies of general pharmacology, genotoxicity and carcinogenic potential, reveal no special hazard for humans. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration. The changes observed in these studies with the combination medicine were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea – N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages).

There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F₁ generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal effects, including renal toxicity and foetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Pregelatinised maize starch
Magnesium stearate [vegetable]
Hypromellose
Hyprolose
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25 °C.

Protect from light.

6.5 Nature and contents of container

Al/Al blister.

Pack size: 28 film-coated tablets

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG

Prinzregentenstr. 79

81675 München

Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

72742.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

28.06.2010

10. DATE OF REVISION OF THE TEXT

02/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.