SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LOSA-FAR PLUS, Losartan Potassium 50 mg and Hydrochlorothiazide 12.5 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide .
Excipients with known effect:
Ponceau 4R aluminium lake (E124).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Film-coated,yellow,oblong shaped tablets scored on both sides. The score line is intended only tofacilitate the division, to help swallowing, not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LOSA-FAR PLUS is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled by losartan or hydrochlorothiazide alone (see sections 4.3, 4.4, 4.5 and 5.1).

4.2. Posology and method of administration

Hypertension

Losartan + Hydrochlorothiazide should not be used as an initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.

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

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

The usual maintenance dose of LOSA-FAR PLUS is one tablet of LOSA-FAR PLUS(losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily.

For patients that not respond adequately to LOSA-FAR PLUS (losartan 50 mg/hydrochlorothiazide 12.5 mg) the dosage may be increased to two tablets of LOSA-FAR PLUS(losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily.
The maximum dosage is 2 tablets of LOSA-FAR PLUS (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. In general, the anti-hypertensive effect is achieved within 3 to 4 weeks after initiation of therapy.

Use in patients with renal impairment and patients in haemodialysis

No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan and hydrochlorothiazide tablets are not recommended for patients in haemodialysis. Losartan + Hydrochlorothiazide tablets should 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 and/or sodium depletion should be corrected prior to administration of Losartan + Hydrochlorothiazide tablets.

Use in patients with hepatic impairment
Losartan + Hydrochlorothiazide tablets are contraindicated in patients with severe hepatic impairment (see section 4.3).

Use in the elderly
Dosage adjustment is not usually necessary for the elderly.

Use in children and adolescents (<18 years)
There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

Method of administration

LOSA-FAR PLUS may be administered with other anti-hypertensive agents (see sections 4.3, 4.4,4.5 and 5.1).
LOSA-FAR PLUS should be swallowed with a glass of water.
LOSA-FAR PLUS may be administered with or without food.

4.3. Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Hypersensitivity to sulphonamide-derived substances (such as hydrochlorothiazide)
- Therapy resistant hypokalaemia or hypercalcaemia
- Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- Second and third trimester of pregnancy (see sections 4.4 and 4.6)
- Severe renal impairment (i.e. creatinine clearance <30 ml/min)
- Anuria

The concomitant use of LOSA-FAR PLUS 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

Losartan

Angioedema
Patients with a history of angioedema (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, may occur in patients who are volume- and/or sodium-depleted by intense diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of LOSA-FAR PLUS tablets (see sections 4.2 and 4.3).

Electrolyte imbalance

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Therefore, the plasma concentrations of potassium and creatinine clearancevalues should be closely monitored, in particular patients with heart failure and a creatinineclearance between 30-50 ml/min.

The concomitant use of potassium sparing diuretics, potassium supplements and potassium containing salt substitutes with losartan + hydrochlorothiazide is not recommended (see section 4.5).

Hepatic impairment
Based on pharmacokinetic data, which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, LOSA-FAR PLUSshould be used carefully in patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore losartan must not be administered in
patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Renal function impairment
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function, including renal failure, have been reported (in particular, in patients whose renal functionis dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases inblood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. These changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Renal transplantation
There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to anti-hypertensive medicinalproducts acting through inhibition of the renin-angiotensin system. Therefore, the use of LOSA- FAR PLUS tablets is not recommended.

Coronary heart disease and cerebrovascular disease
As with any anti-hypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Ethnic differences
As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non- blacks. This is possibly due to a higher prevalence of low-renin states in the black hypertensive population.

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 (includingacute 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

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 shouldbe 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).

Hypotension and electrolyte/fluid imbalance
As with all anti-hypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g., volume depletion, hyponatraemia, hypochloraemic alkalosis, hypomagnesaemia or hypokalaemia, which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilution hyponatraemia may occur inoedematous patients in hot weather.

Metabolic or endocrine effects
Thiazide therapy may impair glucose tolerance. Dosage adjustment of anti-diabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may 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 undiagnosed hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride blood levels have been associated with thiazide diuretic therapy.
Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic- induced hyperuricaemia.

Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intra-hepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

LOSA-FAR PLUS is contraindicated for patients with severe hepatic impairment (see sections 4.3 and 5.2).

Other
In patients receiving thiazides, with or without history of allergy or bronchial asthma, hypersensitivity reactions may occur. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Excipients
This medicinal product contains Ponceau 4R aluminium lake (E124), which may cause allergic reactions.

4.5. Interactions with other medicinal products and other forms of interaction

Losartan

Rifampicin and fluconazole have been reported to reduce levels of active metabolite. The clinical consequences of these interactions have not been evaluated.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Concomitant administration is notrecommended.

As with other medicines that affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co- administered with angiotensin II receptor antagonists.

When angiotensin II antagonists are administered simultaneously with non-steroidal anti- inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti- inflammatory doses) and non-selective NSAIDs, attenuation of the anti-hypertensive effect may occur. Concomitant use of angiotensin II antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including the possibility of acute renal failure and an increase on the potassium serum levels, especially in patients with pre-existent kidney dysfunction.

The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

In some patients with compromised renal function who are being treated with non-steroidal anti-inflammatory drugs, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists may result in a further deterioration of renal function. These effects are usually reversible.

Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren isassociated 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 inducing hypotension like tricyclic antidepressants, antipsychotics, baclofene, amifostine: concomitant use with these drugs that lower blood pressure, as main or side-effect, may increase the risk of hypotension.

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

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

Anti-diabetic drugs (oral agents and insulin)
Treatment with a thiazide may influence glucose tolerance. Dosage adjustment of the anti-diabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other anti-hypertensive drugs
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 to hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 per cent, respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalaemia.

Vassopressor amines (e.g., adrenaline)
Possible decreased response to vassopressor amines, but not sufficient to avoid their use.

Skeletal muscle relaxants, non-depolarizing (e.g., tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (e.g. probenecid, sulfinpyrazone,allopurinol)

Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be required. Co-administration of a thiazide may increase the incidence of hypersensitivity reactions toallopurinol.

Anti-cholinergic agents (e.g. atropine, biperiden)
Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying velocity.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)
Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

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

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

Ciclosporin
Concomitant treatment with ciclosporin 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.

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium and ECG is recommended when Losartan + Hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and anti-arrhythmics) and with torsades de pointes inducers (ventricular tachycardia), and hypokalaemia is a predisposing factor to torsades de pointes (ventricular tachycardia):
- Class Ia anti-arrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III anti-arrhythmics (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 IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

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.

Laboratory Test Interactions
Due to their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (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 product. Patients should be rehydrated before the administration.

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

Angiotensin II Receptor Antagonists (AIIRAs):
The use of AIIRAs is not recommended during the first trimester of pregnancy (see section 4.4). The use of ARA is contra-indicated during the 2nd and 3rd trimester of pregnancy (see sections 4.3and 4.4).
Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor inhibitors (AIIRAs), similar risks may exist for this class of medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments with an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRA should be stopped immediately and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy 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 section 5.3).
Should exposure to AIIRA have occurred from the second trimester of pregnancy, ultrasound checkof renal function and skull is recommended.
Infants whose mothers have taken ARA should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide:
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third trimesters may compromise fetoplacental perfusion and may cause foetal or neonatal effects like jaundice, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre- eclampsia due to the increased risk of decreased plasma volume and placental hypoperfusion, without a beneficial

effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women, except in rare situations where no alternative treatment could be used.

Breast-feeding

Angiotensin II Receptor Antagonists (AIIRAs):
Because no information is available regarding the use of LOSA-FAR PLUS during breastfeeding, LOSA-FAR PLUS is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in breast milk in small amounts. Thiazides, when used in high doses that cause intense diuresis, may inhibit milk production. The use of LOSA-FAR PLUS duringbreast-feeding is not recommended. If LOSA-FAR PLUS is used during lactation, the doses shouldbe 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 use machines have been performed.

However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking anti-hypertensive therapy, in particular during initiation of treatment or when the 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:	≥ 1/10
Common:	≥ 1/100, < 1/10
Uncommon:	≥ 1/1,000, < 1/100
Rare:	≥ 1/10,000, < 1/1,000
Very rare:	< 1/10,000
Not known:	cannot be estimated from the available data

In clinical trials with losartan potassium salt and hydrochlorothiazide, no adverse reactions specific to this combination of substances were observed. The adverse reactions were restricted to those that were formerly observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials for essential hypertension, dizziness was the only adverse reaction reported as substance-related that occurred with an incidence greater than placebo in 1% or more of patients treated with losartan and hydrochlorothiazide.

In addition to these effects, there are further adverse reactions reported after the introduction of theproduct to the market as follows:

<u>Hepato-biliary disorders</u>
Rare: Hepatitis

<u>Investigations</u>
Rare: Hyperkalaemia, increase in ALT

Additional adverse reactions that have been seen with one of the individual components and maybe potential adverse reactions with losartan potassium/hydrochlorothiazide are the following:

Losartan:

Blood and lymphatic system disorders
Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysisNot known: Thrombocytopenia

Cardiac disorders

Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus

Eye disorders
Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Gastrointestinal disorders
Common: Abdominal pain, nausea, diarrhoea, dyspepsia
Uncommon: Constipation, dental pain, dry mouth, flatulence, gastritis, vomiting
Not known: Pancreatitis

General disorders and administration site condition changes
Common: Asthenia, fatigue, chest pain
Uncommon: Facial oedema, oedema, feverNot known: Flu-like symptoms, malaise

Hepato-biliary disorders
Not known: Liver function abnormalities.

Immune system disorders
Rare: Hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors.

Metabolism and nutrition disorders
Uncommon: Anorexia, gout

Muscoskeletaland connective tissue disorders
Common: Muscle cramp, back pain, lower limbs pain, myalgia
Uncommon: Upper limbs pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain,stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness
Not known: Rhabdomyolysis

Nervous system disorders
Common: Headache, dizziness
Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncopeNot known: Dysgeusia

Psychiatric disorders
Common: Insomnia

Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams,sleep disorder, drowsiness, memory impairment

Renal and urinary disorders
Common: Renal impairment, renal insufficiency
Uncommon: Nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders
Uncommon: Decreased libido, erectile dysfunction/impotence

Respiratory, thoracic and mediastinal disorders
Common: Cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis,respiratory congestion

Skin and subcutaneous tissue disorders:
Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash,urticaria, sweating

Vascular disorders
Uncommon: Vasculitis
Not known: Dose-related orthostatic effects

Investigations
Common: Hyperkalaemia, mild reduction of haematocrit and haemoglobin
Uncommon: Mild increase in urea and creatinine serum levels
Very rare: Increase in hepatic enzymes and bilirubinNot
known: Hyponatremia

Hydrochlorothiazide

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cellcarcinoma)

Blood and lymphatic system disorders
Uncommon: Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia

Immune system disorders
Rare: Anaphylactic reaction

Metabolism and nutrition disorders
Uncommon: Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia

Psychiatric disorders
Uncommon: Insomnia

Nervous system disorders
Common: Cephalalgia

Eye disorders
Uncommon: Transient blurred vision, xanthopsia

Vascular disorders
Uncommon: Necrotizing angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders
Uncommon: Respiratory distress including pneumonitis and pulmonary oedema

Gastrointestinal disorders:
Uncommon: Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation

Hepato-biliary disorders
Uncommon: Icterus (intrahepatic cholestatis), pancreatitis

Skin and subcutaneous tissue disorders
Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysisNot known: Cutaneous Lupus Erythematosus

Muscoskeletaland connective tissue disorders
Uncommon: Muscle cramps

Renal and urinary disorders
Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditionsUncommon:
Fever, dizziness

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after marketing authorisation is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9. Overdose

No specific information is available on the treatment of overdosage with LOSA-FAR PLUS. Treatment is symptomatic and supportive. Therapy with LOSA-FAR PLUS should be discontinued and the patient observed closely. Suggested measures include induction of vomit 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 overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic(vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor the active metabolite can be removed by haemodialysis.

Hydrochlorothiazide
The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

Pharmacotherapeutic group: 3.4.2.2 Cardiovascular system. Anti-hypertensive agents. Modifiers ofthe renin-angiotensin system. Angiotensin receptor antagonists.
ATC code: C09CA01.

Losartan + Hydrochlorothiazide

The components of LOSA-FAR PLUS have been shown to have an additive effect on blood- pressure reduction, reducing blood pressure to a greater degree than either component alone. Thiseffect is thought to be a result of the complimentary actions of both components. Further, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, decreases serum potassium, and increases the levels of angiotensin II. Administration of losartan blocks all the physiologically relevant actions of angiotensin II and through inhibition of aldosterone could tend to attenuate the potassium loss associated with the diuretic.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause modest increases in uric acid; the combination of the two substances tendsto attenuate the diuretic-induced hyperuricaemia.

The anti-hypertensive effect of LOSA-FAR PLUS is sustained for a 24-hour period. In clinical studies of at least 1 year's duration, the anti-hypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of losartan + hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.

LOSA-FAR PLUS is effective in reducing blood pressure in males and females, blacks and non- blacks and in younger (<65 years) and older (>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 found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys, and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth-muscle cell proliferation.

Losartan selectively blocks the AT1 receptor. *In vitro* and *in vivo*, both losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of its source or route of synthesis.

Losartan does not have an agonist effect, nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore, losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.

During administration of losartan, the removal of the angiotensin II negative feedback on renin secretion leads to increased plasma-renin activity. These increases in plasma-renin activity lead to increases in angiotensin II in plasma. Despite these increases, the anti-hypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating an effective angiotensin II receptor blockade. After discontinuation of losartan, plasma-renin activity and angiotensin II values lowered within three days to baseline values.

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

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

In non-diabetic hypertensive patients with proteinuria, the administration of losartan potassium significantly reduces proteinuria, fractional excretion of albumin and IgG. Losartan maintains glomerular filtration rate and reduces filtration fraction. Generally losartan causes a decrease in serum uric acid (usually <0.4 mg/dl), which was persistent in chronic therapy.

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

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan produced positive haemodynamic and neurohormonal effects characterized by an increase in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate and a reduction in circulating levels of aldosterone and norepinephrine, respectively. 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. Measurement of blood pressure 24 hours post-dose relative to 5-6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood-pressure reduction at the end of the dosing interval was approximately 70-80% of the effect seen 5-6 hours post-dose.

Discontinuation of losartan in hypertensive patients did not result in an abrupt rise in bloodpressure. Despite the marked decrease in blood pressure, losartan had no clinically significant effect on heart rate.

Losartan is equally effective in males and females, and in younger (<65 years) and older (>65 years) hypertensive patients.

LIFE Study

The “Losartan Intervention For Endpoint reduction in hypertension (LIFE)” study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other anti-hypertensives, with the exception of ACE inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up 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 lowered to similar levels in the two groups. Treatment withlosartan resulted in a 13.0% risk reduction (p=0.021, 95 % confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

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

Two large randomised, controlled trials (ONTARGET (ONgoingTelmisartanAlone and in combination with Ramipril Global Endpoint Trial) and VANEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) haveexamined the use of the combination of an ACE-inhibitor with an angiotensinII receptor blocker.

ONTARGET was a study conducted in patients with a history ofcardiovascular or cerebrovascular disease, or type 2 diabetes mellitusaccompanied by evidence of end-organ damage. VA NEPHRON-D was astudy in patients with type 2 diabetes mellitus and diabetic nephropathy.

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

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular andRenal Disease Endpoints) was a study designed to test the benefit of addingaliskiren to a standard therapy of an ACE- inhibitor or an angiotensin IIreceptor blocker in patients with type 2 diabetes mellitus and chronic kidneydisease, cardiovascular disease, or both. The study was terminated earlybecause of an increased risk of adverse outcomes. Cardiovascular death andstroke were both numerically more frequent in the aliskiren group than in theplacebo group and adverse events and serious adverse events of interest(hyperkalaemia, hypotension and renal dysfunction) were more frequentlyreported in the aliskiren group than in the placebo group.

Hydrochlorothiazide

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

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours;the effect persists for up to 24 hours.

Non-melanoma skin cancer:
Based on available data from epidemiological studies, cumulative dosedependentassociation between HCTZ and NMSC has been observed. One study included a populationcomprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with anadjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clearcumulative dose response relationship was observed for both BCC and SCC. Another study showed apossible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer werematched with 63,067 population controls, using a risk-set sampling strategy. A cumulative doseresponserelationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR3.9 (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, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when the drug was administered with a standardised meal.

Distribution

Losartan
Both 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 placental but not the blood-brain barrier and is excreted in breastmilk.

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 ^{14}C-labelled losartan potassium, circulating plasma radioactivity is attributed primarily to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one per cent of individuals 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, an N-2 tetrazole glucuronide.

Elimination

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

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

Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labeled losartan in man, about 35% of radioactivity is recovered in the urine and 58% in the faeces.
Hydrochlorothiazide
Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidneys. When plasma levels have been followed 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.

Characteristics in patients

Losartan + Hydrochlorothiazide
The plasma concentrations of losartan and its active metabolite and the absorption of hydrochlorothiazide in elderly hypertensives are not significantly different from those in young hypertensives.

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

Pharmacokinetic studies have shown that the AUC of losartan is no different in healthy Japanese and non-Japanese male subjects. However, the AUC of the carboxylic acid metabolite (E-3174) appears to be different between the two groups, with about 1.5-fold higher exposure in Japanese individuals than in non-Japanese individuals. The clinical significance of these results is unknown.

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

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to 6 months duration inrats and dogs after oral administration, and the changes observed in these studies with the combination 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 and 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

Tablet core:
Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Povidone
Magnesium stearate.

Tablet film-coating:
Hipromelose 2910,
Macrogol 6000,
Talc,
Simethicone,
Titanium Dioxide (E171),
Quinoline Yellow Aluminium Lake (E104),
Ponceau 4R Aluminium Lake (E124).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 30ºC.

Store in the original package to protect from light and moisture. Do not open the blister pack that contains the tablet until you are ready to take it.

6.5. Nature and contents of container

The tablets are packed in Alu/Alu blisters.

LOSA-FAR PLUS 50 mg + 12.5 mg is available in packs of 56 film-coated tablets.

6.6. Special precautions for disposal and handling

There are no special requirements.

Any unused medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

GP – GENÉRICOS PORTUGUESES, LDA.
Rua Henrique de Paiva Couceiro, no. 29
Venda Nova, 2700-451 Amadora
Portugal

8. MARKETING AUTHORISATION NUMBER(S)

0574/07795/NMR/2019

9. DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

11/03/2020

10. DATE OF REVISION OF THE TEXT

November 2023