SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LOSARTİL PLUS® 50 mg / 12.5 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Losartan potassium.....50 mg

Hydrochlorothiazide.....12.5 mg

Excipients:

Aggromelate Lactose Monohydrate

(Monohydrate 80)(Made from cow's milk.)…….76.00 mg

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.

Round, slightly convex and light yellow film-coated tablets.

4. CLINICAL PROPERTIES

4.1 4.1. Therapeutic indications

LOSARTIL PLUS is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled with losartan or hydrochlorothiazide alone.

It is used to reduce the risk of cardiovascular morbidity and death in hypertensive patients with left ventricular hypertrophy.

LOSARTIL PLUS is indicated to reduce the risk of stroke in patients with hypertension and left ventricular hypertrophy, but this benefit does not apply to black patients.

Losartan can be used alone or in combination with other antihypertensive agents *(see sections 4.3, 4.4, 4.5 and 5.1)*.

4.2. Posology and method of administration

Posology

Hypertension

Losartan and hydrochlorothiazide are not for use as initial therapy, but are for use in patients not adequately controlled with losartan potassium or hydrochlorothiazide alone.

Dose titration of each ingredient (losartan and hydrochlorothiazide) is recommended.

When clinically appropriate, direct conversion from monotherapy to fixed combination may be considered in inadequately controlled patients.

The usual starting dose is 50 mg losartan / 12.5 mg hydrochlorothiazide film-coated tablet once daily.

Losartan can be used alone or in combination with other antihypertensive agents *(see sections 4.3, 4.4, 4.5 and 5.1).*

Application frequency and duration:

In patients whose blood pressure cannot be adequately controlled with 50 mg losartan / 12.5 mg hydrochlorothiazide, depending on the patient's condition the dose can be increased to two LOSARTIL PLUS 50 mg / 12.5 mg film-coated tablets per day or changed to 100 mg losartan / 25 mg hydrochlorothiazide film-coated tablets once a day. The highest daily dose is 2 tablets of 50 mg losartan / 12.5 mg hydrochlorothiazide or 1 tablet of 100 mg losartan / 25 mg hydrochlorothiazide.

The maximum daily dose combination of 100 mg losartan / 25 mg hydrochlorothiazide should not be exceeded. The antihypertensive effect is seen within 3-4 weeks after the start of treatment.

100 mg losartan / 12.5 mg hydrochlorothiazide Available for patients requiring additional blood pressure control treated with 100 mg losartan.

Method of administration:

For oral use.

LOSARTIL PLUS should be taken with or between meals, swallowed whole with a sufficient amount of water.

Additional information on special populations:

Kidney/Liver failure:

No dosage adjustment is required in patients with moderate renal impairment (creatinine clearance 30-50 ml/min). Losartan and hydrochlorothiazide tablets are not recommended for hemodialysis patients. Losartan/hydrochlorothiazide tablets should not be used in patients with severe renal dysfunction (creatinine clearance <30 ml/min) (see section 4.3).

LOSARTIL PLUS is contraindicated in patients with severe hepatic impairment (see section 4.3).

Pediatric population:

The safety and effectiveness of LOSARTIL PLUS in pediatric patients have not been demonstrated. Therefore, the use of losartan/hydrochlorothiazide is not recommended in children and young people under 18 years of age.

Geriatric population:

There is usually no need for dosage adjustment in elderly patients.

Other:

Use in patients with intravascular volume depletion

Volume and/or sodium depletion must be corrected before administering losartan/hydrochlorothiazide tablets.

4.3. Contraindications

- Hypersensitivity to losartan, sulfonamide derivatives (such as hydrochlorothiazide) or any of the other ingredients it contains.
- Hypokalemia and hypercalcemia that do not respond to treatment
- Severe liver failure; cholestasis and bile duct obstruction disorders
- Refractory hyponatremia
- Symptomatic hyperuricemia/gout disease
- All trimesters of pregnancy (see sections 4.4 and 4.6).
- Severe renal failure (creatinine clearance < 30 ml/minute)
- Anuria
- Concomitant use of LOSARTIL PLUS 50mg/12.5mg Film-coated Tablet and aliskiren is contraindicated in patients with diabetes mellitus or renal failure (GFR<60 ml/min/1.73 m2) (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 may occur, especially after the first dose, in patients with volume and/or sodium depletion due to excessive diuretic therapy, dietary salt restriction, diarrhea or vomiting. Such conditions must be corrected before administering LOSARTIL PLUS tablets (see sections 4.2 and 4.3).

Electrolyte imbalances

lectrolyte imbalances are common in diabetic and non-diabetic patients with impaired renal function and must be corrected. Accordingly, plasma potassium concentrations and creatinine clearance values should be closely monitored; Especially patients with heart failure and creatinine clearance of 30-50 ml/min should be closely monitored.

Concomitant administration of potassium-sparing diuretics, potassium supplements and potassium salts with losartan/hydrochlorothiazide is not recommended (see section 4.5).

Liver dysfunction

Based on pharmacokinetic data showing a significant increase in plasma losartan concentrations in patients with cirrhosis, LOSARTIL PLUS should be used with caution in patients with a history of mild to moderate liver dysfunction. There is no treatment experience with losartan in patients with severe liver dysfunction. Therefore, LOSARTIL PLUS is contraindicated in patients with severe liver dysfunction (see sections 4.2, 4.3 and 5.2).

Kidney dysfunction

Changes in renal function (including renal failure) due to inhibition of the renin-angiotensin-aldosterone system have been reported; These changes have been observed particularly in patients whose renal function is dependent on the renin-angiotensin-aldosterone system (such as patients with severe heart failure or existing renal dysfunction).

As with other drugs that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have been reported in patients with bilateral renal artery stenosis or arterial stenosis to a single kidney; These changes in renal function may be reversible after treatment is discontinued. Losartan should be used with caution in patients with bilateral renal artery stenosis or artery stenosis to a single kidney.

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

Hypotension, syncope, stroke, hyperkalemia, and changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially with combination use that may affect this system. The use of ARBs or ACE inhibitors together with aliskiren is not recommended because it causes dual blockade of the RAAS The combination with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR<60ml/min/1.73 m2) (see section 4.3).

Kidney transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism generally do not respond to antihypertensive drugs that act through inhibition of the renin-angiotensin system. Therefore, the use of LOSARTIL PLUS tablets is not recommended in these patients.

Coronary heart disease and cerebrovascular disease

As with other antihypertensive agents, excessive blood pressure reduction in patients with ischemic cardiovascular and cerebrovascular disease may lead to myocardial infarction or stroke.

Heart failure

As with other drugs that affect the renin-angiotensin system, in patients with heart failure (with or without renal dysfunction), there is a risk of severe arterial hypotension and (usually acute) renal dysfunction.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilator drugs, extreme caution should be exercised in patients with aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy.

Ethnic differences

As observed with angiotensin-converting enzyme inhibitors, losartan and other angiotensin antagonists are significantly less effective in lowering blood pressure in black patients because the prevalence of low renin levels is higher in the black hypertensive population.

Pregnancy

LOSARTIL PLUS should not be started during pregnancy. Unless continued losartan/hydrochlorothiazide therapy is considered essential, patients planning pregnancy should switch to alternative antihypertensive treatments with a documented safety profile for use in pregnancy. Once pregnancy is detected, LOSARTIL PLUS treatment should be discontinued immediately and, if appropriate, alternative treatment should be started (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, syncope, hyperkalaemia and decreased renal function (including acute renal failure). Concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is not recommended, as they lead to dual blockade of the RAAS (see sections 4.5 and 5.1).

If dual blockade therapy is deemed absolutely necessary, it should only be performed under specialist supervision and renal function, electrolytes and blood pressure should be monitored closely and frequently.
ACE-inhibitors and angiotensin II receptor blockers should not be used together in patients with diabetic nephropathy.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive treatments, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, such as volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia, which may occur due to intermittent diarrhea or vomiting. In such patients, serum electrolytes should be measured periodically at appropriate time intervals. Dilutional hyponatremia may occur in patients with edema in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustments of antidiabetic agents, including insulin, may be necessary (see section 4.5). Latent diabetes mellitus may occur during thiazide treatment.
Thiazides may decrease urinary calcium excretion and cause intermittent mild elevations in serum calcium. Marked hypercalcemia may be evidence of subtle hyperparathyroidism.
Thiazides should be discontinued before performing parathyroid function tests.
Thiazide diuretic therapy may be associated with increases in cholesterol and triglyceride levels.
Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Since losartan reduces uric acid, the combination of losartan and hydrochlorothiazide reduces diuretic-induced hyperuricemia.

Liver dysfunction

Thiazides should be used with caution in patients with impaired liver function or progressive liver disease, as thiazides can cause intrahepatic cholestasis and minor changes in fluid and electrolyte balance may precipitate hepatic coma.
LOSARTIL PLUS is contraindicated in patients with severe liver dysfunction (see sections 4.3 and 5.2).

Non-melanoma skin cancer

In two epidemiological studies based on the Danish National Cancer Registry; An increased risk of non-melanoma skin cancer [basal cell carcinoma and squamous cell carcinoma] has been observed with increasing cumulative hydrochlorothiazide exposure. The photosensitizing effect of hydrochlorothiazide may play a role as a possible mechanism in non-melanoma skin cancer.

Patients taking hydrochlorothiazide should be informed about the risk of non-melanoma skin cancer and should be advised to check their skin regularly for new lesions and to promptly report suspicious skin lesions. Patients should be advised to limit exposure to sunlight and UV light and to apply adequate protection in case of exposure to minimize the risk of skin cancer. Suspicious skin lesions should be examined urgently, including histological biopsy examinations. The use of hydrochlorothiazide may also need to be carefully reconsidered in patients with a history of non-melanoma skin cancer. (see also Section 4.8).

Other

Hypersensitivity reactions may occur in patients taking thiazide, with or without a history of allergy or bronchial asthma. Activation or worsening of systemic lupus erythematosus has been reported during use of thiazides.

This medicinal product contains less than 1mmol (39 mg) potassium per dose; So it doesn't actually contain potassium.

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

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

Losartan

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

As with other drugs that block angiotensin II or its effects, potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or potassium salts may cause increases in serum potassium. Concomitant administration is not recommended.

As with other drugs that affect sodium excretion, lithium excretion may be decreased. Therefore, serum lithium levels should be closely monitored if lithium salts are administered concomitantly with angiotensin II receptor antagonists.

A decrease in the antihypertensive effect may occur when angiotensin II antagonists are administered with NSAIDs (selective COX-2 inhibitors, acetylsalicylic acid at anti-

inflammatory doses) and non-selective NSAIDs. Concomitant use of angiotensin II antagonists or diuretics with NSAIDs may lead to elevations in serum potassium and an increased risk of worsening renal function (including possible acute renal failure), especially in patients with already impaired renal functionThis combination should be administered with caution, especially to the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiating concomitant therapy and periodically thereafter.

In some patients with impaired renal function being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, coadministration of angiotensin II receptor antagonists may further worsen renal function. These effects are usually reversible.

Dual-blockade (e.g. adding an ACE inhibitor or aliskiren to the angiotensin II receptor) should be limited to individual cases requiring close monitoring of blood pressure, renal function and electrolytes. Some studies have shown that dual blockade of the renin-angiotensin-aldosterone system was associated with hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to a single renin-angiotensin-aldosterone system agent in patients with established atherosclerotic disease, heart failure, or diabetes resulting in organ damage. showed a higher correlation with its use.

Other substances that induce hypotension, such as tricyclic antidepressants, antipsychotics, baclofen, amifostine: Concomitant use of these drugs that lower blood pressure may increase the risk of hypotension as a side effect or main effect.

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

Hydrochlorothiazide

The following drugs may interact with thiazide diuretics when administered concomitantly:

Alcohol, barbiturates, narcotics or antidepressants

An increase in orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)

Thiazide treatment may affect glucose tolerance. Adjustment in dosage of antidiabetic medication may be required. Metformin should be used with caution due to the risk of lactic acidosis due to possible functional renal failure associated with hydrochlorothiazide.

Other antihypertensive drugs

Additive effect.

Cholestyramine and colestipol resins:

The absorption of hydrochlorothiazide is impaired in the presence of anion-exchanging resins. Single doses of cholestyramine or colestipol resins bind to hydrochlorothiazide, reducing the absorption of this drug from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH

Exacerbation of electrolyte deficiency (especially hypokalemia).

Pressor amines (e.g. adrenaline)

There is a possible reduction in response to pressor amines, but this decrease is not large enough to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine) neuromuscular blockers

There is a possible increase in response to muscle relaxants.

Lithium

Diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity; Concomitant use is not recommended.

Medicinal products used to treat gout (probenecid, sulfinpyrazone and allopurinol)

Since hydrochlorothiazide may increase serum uric acid levels, dosage adjustments of uricosuric medicinal products may be necessary. The dosage of probenecid or sulfinpyrazone may need to be increased. Concomitant administration of thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)

They may increase the bioavailability of thiazide-type diuretics through a decrease in gastrointestinal motility and an increase in gastric emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates

In the presence of high doses of salicylates, hydrochlorothiazide may increase the toxic effect of salicylates on the central nervous system.

Methyldopa

There are isolated reports of hemolytic anemia occurring with concurrent use of hydrochlorothiazide and methyldopa.

Cyclosporine

Concomitant cyclosporine therapy may increase the risk of hyperuricemia and gout-type complications.

Digital glycosides

Thiazide-induced hypokalemia or hypomagnesemia may accelerate the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disorders

Periodic monitoring of serum potassium level and ECG is recommended when losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disorders (e.g. digitalis glycosides and antiarrhythmics) and medicinal products that induce Torsades de Pointes (ventricular tachycardia) (some antiarrhythmics): Hypokalemia is 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 I.V., halofantrine, mizolastine, pentamidine, terfenadine, vincamine I.V.).

Calcium salts

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

Interactions with laboratory tests

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

Carbamazepine

There is a risk of symptomatic hyponatremia. Clinical and biological follow-up is required.

Iodinated contrast medium

The risk of acute renal failure increases in diuretic-induced dehydration, especially with high doses of iodine product. Patients should be rehydrated before application.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulating laxatives or glycyrrhizin (found in licorice)

Hydrochlorothiazide may aggravate electrolyte imbalance, especially hypokalemia.

Use with Aliskiren:

The use of ARB and ACE inhibitors with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR<60 ml/min/1.73m2) (see sections 4.3 and 4.4).

Additional information regarding special populations

No clinical interaction studies have been conducted in special populations.

Pediatric population:

No clinical interaction studies have been conducted in the pediatric population.

4.6. Pregnancy and lactation

General advice

Pregnancy category D for all trimesters of pregnancy.

Women with childbearing potential/Birth control (Contraception)

Before a planned pregnancy, a suitable alternative treatment should be switched.

Pregnancy period

The use of LOSARTIL PLUS is contraindicated in all trimesters of pregnancy (see sections 4.3 and 4.4).

Epidemiological evidence indicating a risk of teratogenicity after exposure to ACE inhibitors during the first trimester of pregnancy is inconclusive; however, a small increase in risk cannot be excluded. Although no controlled epidemiological data are available on the risk with Angiotensin II Receptor Blockers (ARBs), similar risks may exist for this class of drugs. Unless continued ARB therapy is considered essential, patients planning pregnancy should switch to alternative antihypertensive treatments with a documented safety profile for use in pregnancy. As soon as pregnancy is detected, LOSARTIL PLUS treatment should be stopped immediately and, if appropriate, alternative treatment should be started.

Exposure to LOSARTIL PLUS therapy during the 2nd and 3rd trimesters of pregnancy is known to induce fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) in humans (see section 5.3).

If exposed to LOSARTIL PLUS during the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Babies whose mothers have used LOSARTIL PLUS should be carefully observed for hypotension (see also sections 4.3 and 4.4).

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide in pregnancy, especially in the first trimester. Animal studies are not sufficient.

Hydrochlorothiazide crosses the placenta. Due to the pharmacological mechanism of action of hydrochlorothiazide, its use in the 2nd and 3rd trimesters may compromise feto-placental perfusion and lead to effects such as thrombocytopenia, electrolyte imbalance and icterus in the fetus and newborn.

Hydrochlorothiazide should not be used for gestational edema, gestational hypertension or preeclampsia due to the risk of plasma volume reduction and hypoperfusion of the placenta and lack of a beneficial effect on the disease course.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women, except in rare cases where no other alternative treatment can be used.

Lactation period

There is no information regarding the use of LOSARTIL PLUS during breastfeeding. Hydrochlorothiazide passes into breast milk. Therefore, LOSARTIL PLUS is not recommended during breastfeeding. Alternative treatments with known better safety profiles should be preferred during breastfeeding, especially when breastfeeding newborn or premature babies.

Hydrochlorothiazide

Hydrochlorothiazide passes into breast milk in very small amounts. High doses of thiazides cause intense diuresis, which suppresses milk production. LOSARTIL PLUS is not recommended for use during breastfeeding. If LOSARTIL PLUS is to be used during breastfeeding, the lowest dose should be preferred.

Reproductive ability/Fertility

There is no sufficient data regarding the reproductive ability of LOSARTIL PLUS in humans.

4.7. Effects on the ability to drive and use machines

No studies have been conducted examining the effects on the ability to drive and use machines. However, it should be kept in mind that dizziness or drowsiness may occasionally occur while driving or using machines, while taking antihypertensives, and especially when starting treatment or increasing the dose.

4.8. Undesirable effects

Adverse events are listed below by system organ class. Frequencies are defined as follows:

In different organ systems;

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 studies with losartan potassium salt and hydrochlorothiazide, no adverse events specific to this combination of substances were observed. Adverse events are limited to those previously observed with losartan potassium salt and/or hydrochlorothiazide.

In controlled clinical trials examining essential hypertension, dizziness was the only adverse event reported to be substance-related, occurring in 1% or more of patients treated with losartan and hydrochlorothiazide, with a higher incidence than placebo.

Benign neoplasms, malignant and unspecified (including cysts and polyps) (with the use of Hydrochlorothiazide)

In addition to these effects, the following adverse reactions have been reported since the product was placed on the market:

Hepato-biliary diseases

Rare: Hepatitis

Studies

Rare: Hyperkalemia, increase in ALT enzyme

Other adverse events that have occurred with one of the individual components and may be potential adverse events of losartan potassium/hydrochlorothiazide:

Losartan

Blood and lymph system diseases

Uncommon: Anemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Unknown: Thrombocytopenia

Immune system diseases

Rare: Hypersensitivity: anaphylactic reactions, angioedema of the face, lips, pharynx and/or tongue causing airway obstruction, including swelling of the larynx and glottis, angioedema

has been reported in the past in some patients with the administration of other drugs, including ACE inhibitors.

Metabolism and nutritional diseases

Uncommon: Anorexia, gout

Psychiatric diseases

Common: Insomnia

Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreaming, sleep disorder, somnolence, memory loss

Nervous system diseases

Common: Headache, dizziness

Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Unknown: Dysgeusia

Eye diseases

Uncommon: blurred vision, burning/stinging in the eye, conjunctivitis, decreased visual acuity

Ear and inner ear diseases

Uncommon: Vertigo, tinnitus

Cardiac diseases

Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, second degree AV block, cerebrovascular accident, myocardial infarction, palpitations, arrhythmia (atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia and ventricular fibrillation).

Vascular diseases

Uncommon: Vasculitis

Unknown: Dose-related orthostatic effects

Respiratory, thoracic and mediastinal diseases

Common: Cough, upper respiratory tract infection, nasal congestion, sinusitis, sinus discomfort.

Uncommon: Pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory distress.

Gastrointestinal diseases

Common: Abdominal pain, nausea, diarrhoea, dyspepsia

Uncommon: Constipation, toothache, dry mouth, flatulence, gastritis, vomiting, resistant constipation

Unknown: Pancreatitis

Hepato-biliary diseases

Rare: Liver inflammation

Not known: Liver function abnormalities

Skin and subcutaneous tissue diseases

Uncommon: Alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal system, connective tissue and bone diseases

Common: Muscle cramps, back pain, leg pain, myalgia

Uncommon: Arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness

Unknown: Rhabdomyolysis

Kidney and urinary tract diseases

Common: Renal disorder, renal failure

Uncommon: Nocturia, increased urinary frequency, urinary tract infection

Reproductive system and breast diseases

Uncommon: Decreased libido, erectile dysfunction/impotence

General disorders and diseases related to the application site

Common: Asthenia, fatigue, chest pain

Uncommon: facial edema, oedema, fever

Unknown: Flu-like symptoms, fatigue

Studies

Common: Hyperkalaemia, slight decrease in hematocrit and hemoglobin, hypoglycemia

Uncommon: Slight increase in serum levels of urea and creatinine.

Very rare: Increased liver enzymes and bilirubin.

Unknown: Hyponatremia

<u>Hydrochlorothiazide</u>

Blood and lymph system diseases

Uncommon: Agranulocytosis, aplastic anemia, haemolytic anemia, leukopenia, purpura thrombocytopenia

Immune system diseases

Rare: Anaphylactic reactions

Metabolism and nutritional diseases

Uncommon: Anorexia, hyperglycaemia, hyperuricemia, hypokalaemia, hyponatremia

Psychiatric diseases

Uncommon: Insomnia

Nervous system diseases

Common: Headache

Eye diseases

Uncommon: Transient blurred vision, xanthopsia.

Vascular diseases

Uncommon: Necrotizing angiitis (vasculitis and cutaneous vasculitis)

Respiratory, thoracic disorders and mediastinal diseases

Uncommon: Respiratory distress including pneumonia and pulmonary edema

Gastrointestinal diseases

Uncommon: Sialadenitis, spasms, gastric irritation, nausea, vomiting, diarrhoea, constipation.

Hepato-biliary diseases

Uncommon: Jaundice (intrahepatic cholestasis), pancreatitis

Skin and subcutaneous tissue diseases

Uncommon: Photosensitivity, urticaria, toxic epidermal necrolysis

Unknown: Cutaneous lupus erythematosus, non-melanoma skin cancer (basal cell carcinoma and Squamous cell carcinoma)

Skeletal-muscular system, connective tissue and bone diseases

Skeletal-muscular system, connective tissue and bone diseases

Kidney and urinary tract diseases

Uncommon: Glycosuria, interstitial nephritis, renal dysfunction, renal failure

General diseases

Uncommon: Fever, dizziness

Description of selected side effects

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

4.9. Overdose and its treatment

There is no specific information regarding the treatment of LOSARTIL PLUS overdose. Treatment is symptomatic and supportive. LOSARTIL PLUS treatment should be discontinued and the patient should be observed closely. Recommended methods include induction of vomiting if overdosage has occurred recently and correction of dehydration, electrolyte imbalance, hepatic coma and hypotension by known procedures.

Losartan

Data on overdose in humans are limited. The most likely signs of overdose are hypotension and tachycardia; bradycardia may result from parasympathetic (vagal) stimulation. If symptomatic hypotension occurs, supportive treatment should be administered.

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

Hydrochlorothiazide

The most common symptoms and findings observed are events resulting from electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration due to excessive diuresis. Hypokalemia may increase cardiac arrhythmias if digitalis has also been administered.

The extent to which hydrochlorothiazide can be removed by hemodialysis has not been determined.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: It is a combination of angiotensin II antagonists (losartan) and diuretics (hydrochlorothiazide).

ATC code: C09DA01

Losartan-hydrochlorothiazide

It has been shown that LOSARTIL PLUS components have an additive effect on lowering blood pressure, reducing blood pressure more than they could on their own. This effect is thought to be a result of the complementary effects of both components. Additionally, as a result of its diuretic effect, hydrochlorothiazide increases plasma renin activity, increases aldosterone secretion, reduces serum potassium and increases angiotensin II levels. Losartan administration blocks all physiological effects of angiotensin II and thus tends to reduce diuretic-induced potassium loss by also inhibiting aldosterone secretion.

Losartan has been shown to have a mild and transient uricosuric effect. Hydrochlorothiazide has been shown to cause mild elevations in uric acid; The combination of losartan and hydrochlorothiazide tends to reduce diuretic-induced hyperuricemia.
The antihypertensive effect of LOSARTIL PLUS continues for 24 hours. In clinical studies lasting at least one year, the antihypertensive effect was maintained when treatment was continued. Despite the significant reduction in blood pressure, Losartan/hydrochlorothiazide administration did not lead to a clinically significant effect on heart rate. In clinical studies, trough diastolic blood pressure measured in the sitting position was reduced by an average of 13.2 mmHg after 12 weeks of treatment with losartan 50 mg/hydrochlorothiazide 12.5 mg.
LOSARTIL PLUS is effective in lowering blood pressure in men and women, black and non-black races, and young (<65 years) and elderly (≥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 powerful vasoconstrictor, is the primary active hormone of the Renin-Angiotensin system and is an important determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT1 receptor, which is found in many tissues (e.g., vascular smooth muscle, adrenal gland, kidneys, and heart) and causes many important biological effects, including vasoconstriction and aldosterone release. Angiotensin II also stimulates smooth muscle cell proliferation.
Losartan selectively binds to the AT1 receptor. In vitro and in vivo, losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all major physiological effects of angiotensin II, regardless of its source or route of synthesis.
Losartan does not block, and has no agonist effect on, ion channels or other hormone receptors important in cardiovascular regulation. Additionally, losartan does not inhibit the ACE (kininase II) enzyme that degrades bradykinin. Accordingly, there is no increase in undesirable effects due to bradykinin.
During losartan administration, the loss of the negative feedback effect of angiotensin II on renin secretion leads to an increase in plasma-renin activity (PRA). The increase in PRA causes an increase in angiotensin II levels in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration persist, indicating effective blockade of the Angiotensin II receptor. After losartan is discontinued, PRA and Angiotensin II values return to baseline values within 3 days. Both losartan and its main active metabolite

have a much higher affinity for the AT1 receptor than for the AT2 receptor. The active metabolite is 10-40 times more active than losartan on a weight basis.

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

Administration of losartan potassium to non-diabetic hypertensive patients with proteinuria significantly reduces proteinuria and the fractional excretion of albumin and IgG. Losartan maintains the glomerular filtration rate and reduces the filtration fraction. In general, losartan causes a decrease in serum uric acid (usually <0.4 mg/dl) and this decrease is maintained with chronic treatment.

Losartan has no effect on autonomic reflexes and has no lasting effect on plasma norepinephrine levels.

In patients with left ventricular failure, 25 mg and 50 mg doses of losartan showed positive hemodynamic and neurohormonal effects; These effects are characterized by increases in cardiac index and decreases in pulmonary capillary wedge pressure, systemic vascular resistance, mean systemic arterial pressure and heart rate (hemodynamic effects) and decreases in circulating levels of aldosterone and norepinephrine (neurohormonal effects). The occurrence of hypotension in these patients with heart failure is dose dependent.

Hypertension studies

In controlled clinical studies, once daily administration of losartan to patients with mild to moderate essential hypertension resulted in statistically significant reductions in systolic and diastolic blood pressure. Blood pressure measurements taken 24 hours postdose compared to measurements taken 5-6 hours postdose showed that blood pressure reduction was maintained for 24 hours; The natural diurnal rhythm is preserved. At the end of the dosing interval, the blood pressure reduction is 70-80% of the effect seen 5-6 hours after the dose.

Discontinuation of losartan in hypertensive patients did not lead to rebound blood pressure. Despite the significant reduction in blood pressure, losartan did not cause clinically significant effects on heart rate.

Losartan is equally effective in men and women and in young (under 65 years of age) and elderly hypertensive patients.

LIFE study

The Losartan Treatment for Endpoint Reduction in Hypertension (LIFE) study was a randomized, triple-blind, active-controlled study conducted in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left ventricular hypertrophy. Patients were randomized to receive losartan 50 mg or atenolol 50 mg once daily. When target blood pressure (<140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was first added and then, if necessary, the dose of losartan or atenolol was increased to 100 mg per day. When necessary to achieve target blood pressure, other antihypertensive agents other than ACE inhibitors, angiotensin II antagonists, or beta-blockers were included in the treatment.

The average follow-up period is 4.8 years.

The primary end point was the composite of cardiovascular morbidity and mortality, measured by the reduction in the combined incidence of cardiovascular death, stroke, and myocardial infarction. Blood pressure decreased significantly to similar levels in the two groups. Losartan treatment provided a 13% risk reduction compared to atenolol in patients who met the primary composite endpoint (p=0.021, 95% confidence interval 0.77-0.98). This reduction was mainly due to a decrease in the incidence of stroke. Losartan treatment reduced the risk of stroke by 25% compared to atenolol (p=0.001, 95% confidence interval 0.63-0.89). Cardiovascular death and myocardial infarction rates are not significantly different between treatment groups.

Two large randomized controlled trials (ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) examined the use of an ACE-inhibitor in combination with an angiotensin II receptor blocker.

The ONTARGET study was conducted in patients with type 2 diabetes mellitus with a history of cardiovascular or cerebrovascular disease or proven end-organ damage. The VA NEPHRON-D study was conducted in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies did not show significant benefit on renal and/or cardiovascular outcomes and mortality, and an increased risk of hyperkalemia, acute kidney injury and/or hypotension was observed compared to monotherapy. Considering their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

Therefore, ACE-inhibitors and angiotensin II receptor blockers should not be used together in patients with diabetic nephropathy.
The ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) study was a study designed to test the benefit of adding aliskiren to the treatment of chronic kidney disease, cardiovascular disease, or an angiotensin II receptor blocker. The study was terminated early due to the increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group compared to the placebo group, and relevant adverse events and serious adverse events (hyperkalemia, hypotension and renal dysfunction) were reported more frequently in the aliskiren group than in the placebo group.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The antihypertensive mechanism of action of thiazide diuretics is not fully known. Thiazides directly increase the excretion of sodium and chloride in approximately equal amounts by affecting the reabsorption mechanisms of electrolytes in the renal tubules. The diuretic effect of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and aldosterone secretion, resulting in increases in urinary potassium and bicarbonate loss and decreases in serum potassium. The renin-aldosterone connection is mediated by Angiotensin II; therefore, concurrent 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 at approximately 4 hours, and continues for 6-12 hours; The antihypertensive effect lasts up to 24 hours.
Non-melanoma skin cancer: Based on available data from epidemiological studies, a cumulative dose-dependent relationship between hydrochlorothiazide and non-melanoma skin cancer has been observed. One study included a population of 71,533 basal cell carcinoma cases and 8629 squamous cell carcinoma cases matched with population controls of 1,430,833 and 172,462, respectively. High levels of hydrochlorothiazide use (≥50,000 mg cumulative) were associated with 1.29 (95% confidence interval (CI): 1.23 – 1.35) for basal cell carcinoma and 3.98 (95% CI: 3.68) for squamous cell carcinoma. It was associated with an adjusted exposure odds ratio (OR) of – 4.31). A significant cumulative dose-response relationship was observed for both basal cell carcinoma and squamous cell carcinoma. Another study showed that lip cancer may be associated with hydrochlorothiazide exposure: 633 lip cancer cases were matched to 63,067 controls using an at-risk-cluster sampling strategy. A cumulative

dose-response relationship has been demonstrated with an adjusted odds ratio (OR) of 2.1 (95% CI: 1.7 – 2.6), with the OR for high long-term users (~25,000 mg) reaching 3.9. (3.0 – 4.9) and increases to 7.7 (5.7 – 10.5) for the highest cumulative dose (~100,000 mg).

5.2. Pharmacokinetic properties

General features

Absorbation:

Losartan

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism to form an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Losartan and its active metabolite reach mean peak concentrations in 1 hour and 3-4 hours, respectively. There was no clinically significant effect on the plasma concentration profile of losartan when taken with a standard meal.

Hydrochlorothiazide

There is not enough data.

Distribution:

Losartan

Losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 liters. Studies in rats show that losartan barely crosses the blood-brain barrier.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placenta, is secreted into breast milk, but cannot cross the blood-brain barrier.

Biotransformation:

Losartan

Approximately 14% of an orally or intravenously administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of C-14-labeled losartan potassium, circulating plasma radioactivity is mainly of losartan and its active metabolite. Minimal conversion of losartan to its active metabolite occurred in approximately 1% of subjects studied.

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

Hydrochlorothiazide

There is not enough data.

Leap:

Losartan

The total plasma clearance of losartan and its active metabolite is approximately 600 ml/min and 50 ml/min, respectively, and the renal clearance is 74 ml/min and 26 ml/min, respectively. When losartan is administered orally, approximately 4% of the dose is detected in the urine unchanged and approximately 6% as its active metabolite. The pharmacokinetics of losartan and its active metabolite are linear up to oral doses of losartan potassium up to 200 mg.

After oral administration, plasma concentrations of losartan and its active metabolite show a multi-exponential decrease. The terminal half-life of losartan is approximately 2 hours and that of its metabolite is 6-9 hours. With a dose of 100 mg once daily, neither losartan nor its active metabolite accumulated significantly in plasma.

Both bile and urinary excretion contribute to the excretion of losartan and its metabolites. After oral administration of 14C-labelled losartan to humans, approximately 35% of the radioactivity was detected in urine and 58% in feces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is rapidly eliminated by the kidney. When plasma levels are monitored for at least 24 hours, plasma half-life is observed to vary between 5.6 and 14.8 hours. At least 61% of the orally administered dose is eliminated unchanged within 24 hours.

Characteristic features of patients

Geriatric:

Losartan- Hydrochlorothiazide

Plasma concentrations of losartan and its active metabolite and absorption of hydrochlorothiazide in elderly hypertensive patients are not significantly different from those in young hypertensive patients.

Kidney/Liver failure:

Losartan

After oral administration to patients with mild-to-moderate alcoholic liver cirrhosis, plasma concentrations of losartan and its active metabolite were approximately 5-fold and 1.7-fold

higher, respectively, than in young male volunteers. Neither losartan nor its active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

There is not enough data.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on classical studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the losartan/hydrochlorothiazide combination was observed in rats and dogs for up to six months. was evaluated after oral administration in ongoing chronic toxicity studies, and the changes observed with this combination in these studies were primarily due to the losartan component. Administration of the losartan/hydrochlorothiazide combination led to a decrease in red blood cell parameters (erythrocytes, hemoglobin, hematocrit), an increase in urea-N in serum, a decrease in heart weight (without histological correlation) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, hemorrhages). There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Fetal toxicity, manifested by a small increase in rib number in the F1 generation, was observed after female rats were treated before and during gestation. As observed in studies with losartan alone, adverse fetal and neonatal effects, including renal toxicity and fetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination in late gestation and/or during lactation.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Microcrystalline Cellulose PH 200

Pregelatinized Corn Starch

Agglomerate Lactose Monohydrate (Monohydrate 80) (Obtained from cow's milk.)

Colloidal Anhydrous Silica

Magnesium Stearate

Kaplama maddesi

Opadry II 85 F 32112 Yellow

Kaplama bileşenleri

Polyvinyl alcohol GL-05FS USP

Titanium Dioxide USP

PEG 3350 Powder EEP
Talk USP
D&C Sarı #10 Aluminum Lacquer

6.2. Incompatibilities

Not reported.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. The nature and content of the packaging

Opaque, PVC/PVDC/Aluminum blister packs containing 28 film-coated tablets.

6.6. Disposal of residues from the medicinal product for human use and other special measures

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulations".

7. LICENSE HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.
Oğuzlar Mah.1370. sok. No: 7/3
Balgat-ANKARA

8. LICENSE NUMBER

212 / 6

9. FIRST LICENSE DATE/ LICENSE RENEWAL DATE

First license date: 11.07.2007
License renewal date: 04.04.2014

10. RENEWAL DATE OF SPC

09/04/2019