Professional Information for ARBILO CO

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ARBILO CO 50/12,5 film-coated tablets

ARBILO CO 100/25 film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARBILO CO 50/12,5: Each tablet contains 50 mg losartan (as potassium) and 12,5 mg hydrochlorothiazide.

ARBILO CO 100/25: Each tablet contains 100 mg losartan (as potassium) and 25 mg hydrochlorothiazide.

Excipients with known effect:

Contains sugar.

ARBILO CO 50/12,5: Each film coated tablet contains 25 mg lactose monohydrate.

ARBILO CO 100/25: Each film coated tablet contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

ARBILO CO 50/12,5: Yellow coloured, oval shaped, film-coated tablets, debossed with ‘J’ on one side and ‘50+’ on the other.

ARBILO CO 100/25: Yellow coloured, oval shaped, film-coated tablets, debossed with ‘J’ on one side and ‘100+’ on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARBILO CO is indicated for the treatment of hypertension in patients established on identical doses of the individual components.

4.2 Posology and method of administration

The maximum dose is one tablet of ARBILO CO (100 mg losartan potassium and 25 mg hydrochlorothiazide) once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.

Special populations

ARBILO CO should not be initiated in patients who are intravascularly volume-depleted (e.g. those treated with high-dose diuretics).

Hepatic or renal impairment

ARBILO CO is not recommended for patients with severe renal impairment or for patients with hepatic impairment (see section 4.4).

Elderly patients

ARBILO CO should not be used as initial therapy in elderly patients.

Method of administration

ARBILO CO may be administered with other antihypertensive medicines, such as calcium channel blockers and beta-blockers.

ARBILO CO may be administered with or without food.

Paediatric population

Safety and efficacy in children have not been established.

4.3 Contraindications

- Hypersensitivity to losartan, hydrochlorothiazide or to any of the components of ARBILO CO listed in section 6.1.
- A history of angioedema related to previous therapy with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance < 30 mL/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics, such as spironolactone, triamterene, amiloride.
- Porphyria.
- Thiazide diuretics in (fixed dose) combination as with ARBILO CO, should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: concomitant administration with ARBILO CO may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see section 4.6).
- Hepatic impairment.
- Therapy resistant hypokalaemia or hypercalcaemia.
- Refractory hyponatraemia.
- Symptomatic hyperuricaemia/gout.
- Anuria.

- The concomitant use of ARBILO CO with aliskiren-containing products is contraindicated (see section 4.4).
- Concomitantly using fluoroquinolones in moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min), and in the elderly.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Pregnancy

Should a woman become pregnant while receiving ARBILO CO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6).

Angioedema

Patients with a history of angioedema (swelling of the face, lips, throat, and/or tongue) should not be given ARBILO CO (see section 4.3).

Hypotension and intravascular depletion

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of ARBILO CO tablets (see sections 4.2 and 4.3) or a lower starting dose should be considered (see section 4.2).

Electrolyte imbalances

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 clearance values should be closely monitored; especially patients with heart failure and a creatinine clearance between 30 – 50 mL/min should be closely monitored.

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. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

The concomitant use of potassium-sparing diuretics, potassium supplements, potassium containing salt substitutes, or other medicines that may increase serum potassium (e.g. trimethoprim-containing products) with losartan/hydrochlorothiazide is not recommended (see sections 4.3 and 4.5).

Hepatic impairment

Pharmacokinetic data demonstrated significantly increased plasma concentrations of losartan in cirrhotic patients. In patients with impaired hepatic function or progressive liver disease, thiazides may cause intrahepatic cholestasis, and minor alterations of fluid and electrolyte balance may precipitate hepatic coma. ARBILO CO is contraindicated for patients with hepatic impairment (see sections 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 function is dependent on the renin-angiotensin-aldosterone system, such as those with severe cardiac insufficiency or pre-existing renal dysfunction).

As with other medicines that affect the renin-angiotensin-aldosterone system, increases in blood 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. ARBILO CO should not be used in patients with bilateral renal artery

stenosis or stenosis of the artery to a solitary kidney (see section 4.3).

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of ARBILO CO tablets is not recommended.

Coronary heart disease and cerebrovascular disease

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 medicines acting on the renin-angiotensin system like ARBILO CO – a risk of severe arterial hypotension, and (often acute) renal impairment.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

ARBILO CO is contraindicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy (see section 4.3).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore contraindicated (see sections 4.3 and 4.5).

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides, as in ARBILO CO, may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium.
Marked hypercalcemia may be evidence of hidden hyperparathyroidism. ARBILO CO should be discontinued before carrying out tests for parathyroid function.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricemia.
Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide, a component of ARBILO CO.

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 exposure has been observed in two epidemiological studies. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking ARBILO CO should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. ARBILO CO should not be used by patients who have had previous and/or current basal cell

carcinomas and/or squamous cell carcinomas of the skin and/or lip (see contraindications).).

Other

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

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists may be less effective in lowering blood pressure in black people than in non-blacks, possibly because higher prevalence of low-renin states in the black hypertensive population.

Fluoroquinolones and ARBs

Concomitant use of fluoroquinolones and ARBs may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ARBs whether used separately and/or concomitantly.

Lactose

ARBILO CO contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ARBILO CO.

4.5 Interaction with other medicines and other forms of interaction

Losartan

No interactions of clinical significance have been identified with hydrochlorothiazide, digoxin, warfarin, cimetidine, phenobarbital, ketoconazole and erythromycin.

Rifampicin and fluconazole have been reported to reduce levels of active metabolite of losartan, as contained in ARBILO CO. The clinical consequences of these interactions have not been

evaluated.

Concomitant use of medicines that block angiotensin II or its effects and potassium-sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, salt substitutes containing potassium, or other medicines that may increase serum potassium (e.g. trimethoprim-containing products) may lead to increases in serum potassium. Co-medication is not advisable (see section 4.3).

Lithium excretion may be reduced. Therefore, co-administration of lithium with ARBILO CO is contraindicated (see section 4.3).

The concomitant use of ARBILO CO and nonsteroidal anti-inflammatory drugs (NSAIDs) (such as selective cyclooxygenase (COX)-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), may result in attenuation of the antihypertensive effect.
Concomitant use of ARBILO CO and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. 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 NSAIDs, including selective cyclooxygenase-2 inhibitors, the co-administration of ARBILO CO 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 is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and

decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting medicine (see sections 4.3 and 4.4).

Other substances inducing hypotension, like tricyclic antidepressants, antipsychotics, baclofen: Concomitant use with these medicines that lower blood pressure, as main or side effect, may increase the risk of hypotension.

Fluoroquinolones

Concomitant use of ARBs and fluoroquinolones may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Hydrochlorothiazide

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

Alcohol, barbiturates, narcotics or antidepressants

Potentiation of orthostatic hypotension may occur.

Antidiabetic medicines (oral medicines and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicine 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 antihypertensive medicines

Additive effect or potentiation.

Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single

doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively. ARBILO CO should therefore be administered one hour before the intake of the resin.

Corticosteroids, adrenocorticotropic hormone (ACTH)

Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g. epinephrine (adrenaline))

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarising (e.g. tubocurarine)

Possible increased responsiveness to the muscle relaxant.

Lithium

Lithium should not generally be given with ARBILO CO. Diuretic medicines reduce the renal clearance of lithium and add a high risk of lithium toxicity. Concomitant use is contraindicated (see section 4.3).

Medicines used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medicines may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic medicines (e.g. atropine, biperiden)

Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic medicines (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicines 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 dysrhythmias.

NSAIDs (including COX-2 inhibitors)

The administration of NSAIDs (including a selective COX-2 inhibitor) can reduce the diuretic, natriuretic and antihypertensive effects of ARBILO CO.

Medicines affected by serum potassium disturbances

Periodic monitoring of serum potassium and electrocardiogram (ECG) is recommended when ARBILO CO is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides and antidysrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicines (including some antidysrhythmics), hypokalaemia being a

predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antidysrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antidysrhythmics (e.g. amiodarone, sotalol).
- Some antipsychotics (e.g. chlorpromazine, trifluoperazine, sulpiride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. erythromycin intravenous, halofantrine, mizolastine).

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

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

Carbamazepine

Risk of symptomatic hyponatremia. 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

Women of childbearing potential

Women of childbearing age should use effective contraception.

Pregnancy

The use of ARBILO CO is contraindicated in pregnancy (see sections 4.3 and 4.4). When pregnancy is planned or confirmed, ARBILO CO should be discontinued.
Medicines affecting the renin-angiotensin system, such as ARBILO CO, can cause embryonal toxicity, fetal and neonatal morbidity and mortality when administered in pregnant women.

Losartan

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 antagonist (AIIRAs), similar risks may exist for this class of medicines. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.

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).

Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken AIIRAs should be closely observed for hypotension (see 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 and appears in cord blood.

Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during second and third trimesters may compromise fetoplacental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopaenia.

Breastfeeding

Safety during lactation has not been established (see sections 4.3 and 4.4).

Because no information is available regarding the use of ARBILO CO during breastfeeding, ARBILO CO is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of ARBILO CO during breastfeeding is contraindicated (see section 4.3).

Fertility

No data are available on the effects of ARBILO CO on fertility.

4.7 Effects on ability to drive and use machines

No studies on the reactions on the ability to drive and use machines have been performed.

However, ARBILO CO may cause dizziness and drowsiness which may affect the ability to drive and use machines, in particular during initiation of treatment or when the dose is increased.

Caution is advised before driving or operating machinery until the effects of ARBILO CO are known.

4.8 Undesirable effects

The following adverse reactions have been reported with the combined use of losartan and hydrochlorothiazide during controlled clinical trials for essential hypertension.

Nervous system disorders

Frequent: dizziness

General disorders and administration site conditions

Frequent: asthenia/fatigue.

The following adverse reactions have been reported in post-marketing experience with the combined use of losartan and hydrochlorothiazide.

Blood and lymphatic system disorders

Frequency unknown: thrombocytopenia

Immune system disorders

Frequency unknown: anaphylactic reactions, angioedema (including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx and/or tongue. Some of these patients previously experienced angioedema with other medicines including ACE inhibitors)

Nervous system disorders

Frequency unknown: dysgeusia (reported with losartan)

Vascular disorders

Frequency unknown: vasculitis (including Henoch-Schönlein purpura)

Respiratory, thoracic and mediastinal disorders

Frequency unknown: cough

Gastrointestinal disorders

Frequency unknown: diarrhoea, vomiting

Hepato-biliary disorders

Less frequent: hepatitis

Skin and subcutaneous tissue disorders

Frequency unknown: urticaria, erythroderma (reported with losartan), photosensitivity

Musculoskeletal and connective tissue disorders

Frequency unknown: arthralgia (reported with losartan)

Investigations

Less frequent: hyperkalaemia, alanine aminotransferase (ALT) increased

The following adverse experiences were reported for losartan during clinical trials and in post-marketing experience.

Infections and infestations

Frequent: upper respiratory infection

Blood and lymphatic system disorders

Less frequent: anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis

Frequency unknown: thrombocytopenia

Immune system disorders

Less frequent: hypersensitivity, anaphylactic reactions, angioedema (including

swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue; in some of these patients, angioedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors)

Metabolism and nutrition disorders

Less frequent: anorexia, gout

Psychiatric disorders

Frequent: insomnia

Less frequent: anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impaired

Nervous system disorders

Frequent: headache, dizziness

Less frequent: nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Frequency unknown: dysgeusia

Eye disorders

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

Ear and labyrinth disorders

Less frequent: vertigo, tinnitus

Cardiac disorders

Less frequent: sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitations, dysrhythmias (atrial fibrillation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)

Vascular disorders

Less frequent: vasculitis, orthostatic hypotension, hypotension

Respiratory, thoracic and mediastinal disorders

Frequent: cough, upper respiratory tract infection, pharyngitis, nasal congestion, sinusitis, sinus disorder

Less frequent: pharyngeal discomfort, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion

Gastrointestinal disorders

Frequent: abdominal pain, nausea, diarrhoea, dyspepsia

Less frequent: constipation, dental pain, xerostomia, flatulence, gastritis, vomiting, obstipation

Frequency unknown: pancreatitis

Hepatobiliary disorders

Frequency unknown: liver function abnormalities

Skin and subcutaneous tissue disorders

Less frequent: alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating

Musculoskeletal and connective tissue disorders

Frequent:	muscle cramps, back pain, leg pain, myalgia
Less frequent:	arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness
Frequency unknown:	rhabdomyolysis

Renal and urinary disorders

Frequent:	renal impairment, renal failure
Less frequent:	nocturia, urinary frequency, urinary tract infection

Reproductive system and breast disorders

Less frequent:	decreased libido, erectile dysfunction/ impotence

General disorders and administration site conditions

Frequent:	asthenia, oedema, chest pain

Investigations

Frequent:	hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia, increased ALT
Less frequent:	mild increase in urea and creatinine serum levels, increase in hepatic enzymes and bilirubin
Frequency unknown:	hyponatraemia

The following adverse experiences were reported for hydrochlorothiazide during clinical trials and in post-marketing experience.

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Frequency unknown:	non-melanoma skin cancer (basal cell carcinoma and squamous cell

carcinoma)

Blood and lymphatic system disorders

Less frequent: agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopaenia

Immune system disorders

Less frequent: anaphylactic reaction

Metabolism and nutrition disorders

Less frequent: anorexia, hyperuricaemia, hyperglycaemia, hypokalaemia, hyponatraemia

Psychiatric disorders

Less frequent: insomnia

Nervous system disorders

Frequent: headache

Less frequent: paraesthesia

Eye disorders

Less frequent: transient blurred vision, xanthopsia

Vascular disorders

Less frequent: necrotising angiitis, vasculitis, cutaneous vasculitis, hypotension (including orthostatic hypotension)

Respiratory, thoracic and mediastinal disorders

Less frequent: respiratory distress (including pneumonitis and pulmonary oedema)

Gastrointestinal disorders

Less frequent: sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation, pancreatitis

Hepatobiliary disorders

Less frequent: jaundice (intrahepatic cholestatic jaundice)

Skin and subcutaneous tissue disorders

Less frequent: photosensitivity, urticaria, toxic epidermal necrolysis, rash

Frequency unknown: cutaneous lupus erythematosus

Musculoskeletal and connective tissue disorders

Less frequent: muscle cramps

Renal and urinary disorders

Less frequent: glycosuria, interstitial nephritis, renal dysfunction, renal failure

General disorders and administration site conditions

Less frequent: fever, dizziness.

Description of selected adverse events

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of ARBILO CO is important. It allows continued monitoring of the benefit/risk balance of ARBILO CO. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of ARBILO CO.

4.9 Overdose

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

Losartan

Limited data are available regarding overdose in humans. The most likely manifestation of overdose 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, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac dysrhythmias.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Other hypotensives.

Pharmacotherapeutic group: Angiotensin-II antagonists, combinations.

ATC code: C09DA01.

Losartan-hydrochlorothiazide

Losartan potassium is an angiotensin II receptor (type AT1) antagonist and hydrochlorothiazide is a diuretic.

The components of ARBILO CO have been shown to have an additive effect on blood pressure reduction, reducing blood pressure to a greater degree than either component alone. This effect 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 losartan and hydrochlorothiazide tends to attenuate the diuretic induced hyperuricemia.

Losartan

Losartan is a synthetically produced oral angiotensin-II receptor (type AT_1) 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 AT_1 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 AT_1 receptor. Both losartan and its pharmacologically active carboxylic acid metabolite (E-3174) block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

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

Both losartan and its principal active metabolite have a far greater affinity for the AT_1 receptor than for the AT_2 receptor.
The active metabolite is 10- to 40-times more active than losartan on a weight for weight basis.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics 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.

5.2 Pharmacokinetic properties

Losartan

Absorption

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 it was administered with a standardised meal.

Distribution

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.

Biotransformation

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 primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent 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

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.
Both biliary and urinary excretion contribute to the elimination of losartan and its metabolites. Following an oral dose of ^{14}C-labelled losartan in man, about 35 % of radioactivity is recovered in the urine and 58 % in the faeces.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk. Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidney. 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.

In a pharmacokinetic interaction study, hydrochlorothiazide 12,5 mg did not alter the pharmacokinetics of losartan 50 mg and vice versa.

Special populations

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

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.

5.3. Preclinical safety data

No further data of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate

Magnesium stearate (E572)

Microcrystalline cellulose (E460)

Pregelatinised starch.

Film-coating:

Opadry yellow (containing hydroxypropyl cellulose (E463), hypromellose (E464), quinoline yellow (E104) and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Silver/grey aluminium/aluminium blister strips placed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Jubilant Pharma SA (Pty) Ltd

24 Parrot Avenue

Extension 1, Lenasia

Johannesburg

1820

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8. REGISTRATION NUMBERS

ARBILO CO 50/12,5: 46/7.1.3/0741

ARBILO CO 100/25: 46/7.1.3/0742

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 April 2022

10. DATE OF REVISION OF THE TEXT

18 June 2025