SCHEDULING STATUS:
S3

PROPRIETARY NAME AND DOSAGE FORM:
LOSARTAN COMP BIOTECH 50/12,5 film-coated tablets
LOSARTAN COMP BIOTECH 100/25 film-coated tablets

COMPOSITION:
Each LOSARTAN COMP BIOTECH 50/12,5 film-coated tablet contains 50 mg losartan potassium and 12,5 mg hydrochlorothiazide.
Each LOSARTAN COMP BIOTECH 100/25 film-coated tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide.
Tablet core: Lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinised starch, colloidal anhydrous silica.
Tablet coating: ferric oxide, hydroxylpropylcellulose, hypromellose, talc, titanium dioxide.
Contains sugar (lactose monohydrate).

PHARMACOLOGICAL CLASSIFICATION:
A 7.1.3 Other hypotensives

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
LOSARTAN COMP BIOTECH is a combination of losartan potassium (an angiotensin II receptor type AT_1 antagonist) and hydrochlorothiazide (a diuretic).
Losartan:
Losartan is a non-peptide angiotensin II receptor antagonist with high affinity and selectivity for the AT_1 receptor, without binding to or blocking other hormone receptors or ion channels important in cardiovascular regulation. Angiotensin II is a potent vasoconstrictor, a primary active hormone of the renin-angiotensin system. Losartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by inhibiting the binding of angiotensin II to the AT_1 receptor.
Losartan is a specific antagonist of the angiotensin II receptor type AT_1; it does not inhibit ACE (kinínase II), the enzyme that degrades bradykinin. Removal of angiotensin II negative feedback on renin secretion leads to increased plasma renin activity during losartan administration. A 2-3-fold increase in angiotensin II in plasma comes as a result of increases in plasma renin activity. However, antihypertensive activity and suppression of plasma aldosterone concentration are apparent, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, plasma renin activity and angiotensin levels declined.
Hydrochlorothiazide:
Hydrochlorothiazide is a diuretic and has antihypertensive properties; the mechanism of the antihypertensive effect of hydrochlorothiazide is unknown. Hydrochlorothiazide does not usually affect normal blood pressure. It affects the distal renal tubular mechanism of electrolyte reabsorption. Hydrochlorothiazide increases excretion of sodium and chloride in approximately equivalent amounts. Natriuresis may be accompanied by some loss of potassium, magnesium and bicarbonate.
After oral use diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.
Losartan Potassium-Hydrochlorothiazide:
Losartan and hydrochlorothiazide are additive in their anti-hypertensive efficacy.
Pharmacokinetic properties
Losartan:
Absorption
Following oral administration, bioavailability of losartan is approximately 33 %. It undergoes first-pass metabolism to form an active carboxylic acid metabolite, which has greater pharmacological activity than losartan, and some inactive metabolites.
Distribution
Both losartan and carboxylic acid metabolite are more than or equal to 99 % bound to plasma proteins. The distribution volume is 34 litres.
Metabolism
About 14 % of an intravenously or orally administered dose is converted to its active metabolite. Mean peak plasma concentrations of losartan and active metabolite occur in 1 hour and 3 to 4 hours, respectively, after an oral dose.
Elimination
Losartan is excreted in the urine, and in the faeces via bile, as unchanged substance and metabolites. Following oral dosing about 35 % of the dose is excreted in the urine and about 60 % in the faeces. The terminal elimination half-life of losartan is 2 hours and its active metabolite is 6 to 9 hours. Neither losartan nor the active metabolite can be removed by haemodialysis. Plasma concentrations of losartan are not altered in patients with impaired renal function and a creatinine clearance above 10 ml/min. Compared to patients with normal renal function, the AUC of losartan is approximately 2-fold greater in patients on haemodialysis.
Hydrochlorothiazide:
Hydrochlorothiazide is not metabolised but is eliminated rapidly by the kidneys.
The plasma half-life has been observed to vary between 5,6 and 14,8 hours after 24 hour observation. At least 61 % of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier.
Losartan Potassium-Hydrochlorothiazide:
Hydrochlorothiazide 12,5 mg does not alter the pharmacokinetics of losartan 50 mg and vice versa.

INDICATIONS:
LOSARTAN COMP BIOTECH is indicated for the treatment of hypertension in patients established on identical doses of the individual agents.

CONTRAINDICATIONS:
- Sensitivity to to any of the components of LOSARTAN COMP BIOTECH.
- A history of angioedema related to previous therapy with 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 less than 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 combination with losartan as in LOSARTAN COMP BIOTECH 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 LOSARTAN COMP BIOTECH may lead to toxic blood concentrations of lithium.
- Pregnancy and lactation (see PREGNANCY AND LACTATION).
- Safety and efficacy has not been established in children.
- Hypersensitivity to other sulphonamide-derived medicines, due to the hydrochlorothiazide component.

WARNINGS AND SPECIAL PRECAUTIONS:
- Women of childbearing age should ensure adequate contraception.

Should a woman become pregnant while receiving LOSARTAN COMP BIOTECH, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see CONTRAINDICATIONS and PREGNANCY AND LACTATION).

- Severe hepatic impairment; cholestasis and biliary obstructive disorders.
- Refractory hyponatraemia.

Hypotension and electrolyte/fluid imbalance:
Symptomatic hypotension may occur in patients who are intravascular volume-depleted (e.g., those treated with high-dose diuretics). These conditions should be corrected prior to administration of LOSARTAN COMP BIOTECH, or a lower starting dose should be used (see DOSAGE AND DIRECTIONS FOR USE).
In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and (less frequently) with acute renal failure and/or death. Similar outcomes are likely with LOSARTAN COMP BIOTECH therapy.
Since hypokalaemia may occur, serum-potassium concentrations should be monitored, especially in the elderly and patients with renal impairment and the concomitant use of potassium-sparing diuretics should generally be avoided (see INTERACTIONS).
Renal and hepatic impairment:
LOSARTAN COMP BIOTECH is not recommended for patients with hepatic impairment or severe renal impairment.
Changes in renal function including renal failure have been reported, due to inhibition of the renin-angiotensin system, these changes in renal function may be reversible upon discontinuation of therapy.
The blood urea and serum creatinine may be increased in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney during treatment with LOSARTAN COMP BIOTECH. These changes in renal function may be reversible upon discontinuation of therapy.
Metabolic and endocrine effects:
Dosage adjustment of anti-diabetic agents, including insulin, may be required (see INTERACTIONS), as thiazide may impair glucose tolerance.
Hydrochlorothiazide in LOSARTAN COMP BIOTECH may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypocalcaemia may be evidence of hidden hyperparathyroidism. LOSARTAN COMP BIOTECH should be discontinued before carrying out tests for parathyroid function.
Increases in cholesterol and triglyceride levels may be associated with hydrochlorothiazide in LOSARTAN COMP BIOTECH. LOSARTAN COMP BIOTECH therapy may precipitate hyperuricaemia and/or gout in certain patients.
Other:
In patients receiving LOSARTAN COMP BIOTECH, sensitivity reactions to thiazides may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematous has been reported with the use of LOSARTAN COMP BIOTECH.
Effects on ability to drive or use machines:
There are no data to suggest that LOSARTAN COMP BIOTECH affects the ability to drive or use machines. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.
Important information about some of the ingredients of LOSARTAN COMP BIOTECH:
LOSARTAN COMP BIOTECH contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take LOSARTAN COMP BIOTECH.

INTERACTIONS:
Losartan Potassium:
The antihypertensive effects of losartan may be potentiated by medicines or other agents that lower blood pressure.
Fluconazole can increase the concentration of losartan.
Non-steroidal anti-inflammatory drugs (NSAIDs) may antagonise the antihypertensive effect of LOSARTAN COMP BIOTECH.
Concurrent use with sympathomimetic may reduce the antihypertensive effects of LOSARTAN COMP BIOTECH.
Potassium-sparing diuretics, potassium containing medication or potassium supplements used concurrently with LOSARTAN COMP BIOTECH may result in hypokalaemia since reduction of aldosterone production induced by LOSARTAN COMP BIOTECH may lead to elevation of serum potassium.
Lithium – see CONTRAINDICATIONS.
Hydrochlorothiazide:
When administered concurrently the following medication may interact with thiazide diuretics:
Alcohol, narcotics or barbiturates:
Potentiation of orthostatic hypotension may occur.
Anti-diabetic agents (oral medicines and insulin):
Dosage adjustment of the anti-diabetic 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.
Antihypertensive medication:
May produce additive hypotensive effect.
Cholestyramine and colestipol resins:
Absorption of hydrochlorothiazide is impaired, single doses of either cholestyramine or colestipol bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively: One hour before the intake of the resin, LOSARTAN COMP BIOTECH should be taken.
Corticosteroids or ACTH:
Concurrent use may intensify electrolyte depletion, particularly hypokalaemia.
Lithium:
Should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.
Sympathomimetic, such as norepinephrine:
May decrease the response to sympathomimetic agents
Skeletal muscle relaxants, non-depolarizing (e.g. tubocurarine): Possible increased responsiveness to the muscle relaxant.
Non-steroidal anti-inflammatory medication:
May reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.
Medicines used in the treatment of gout (probenecid, sulfinpyrazone, allopurinol):
Increased dosage of probenecid or sulfinpyrazone may be necessary. The hydrochlorothiazide in LOSARTAN COMP BIOTECH may increase the incidence of hypersensitivity reactions to allopurinol.
Anticholinergic agents (e.g. atropine, biperiden):
Increase of the bioavailability to hydrochlorothiazide in LOSARTAN COMP BIOTECH by decreasing gastrointestinal motility and stomach emptying rate.
Cytotoxic agents (e.g. cyclophosphamide, methotrexate):
Hydrochlorothiazide in LOSARTAN COMP BIOTECH may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.
Salicylates:
In case of high dosages of salicylates, the hydrochlorothiazide in LOSARTAN COMP BIOTECH may enhance the toxic effect of the salicylates on the central nervous system.
Methyldopa:
There have been reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide as in LOSARTAN COMP BIOTECH and methyldopa.
Ciclosporin:
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.
Digoxin:
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac dysrhythmias.
Medicines affected by serum potassium disturbances, like anti-dysrhythmics, antipsychotics and others:
Periodic monitoring of serum potassium and ECG is recommended when LOSARTAN COMP BIOTECH is administered with medicines affected by serum potassium disturbances.
Calcium salts:
Hydrochlorothiazide as in LOSARTAN COMP BIOTECH may increase serum calcium levels due to decreased excretion. Serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.
Laboratory test interactions:
Because of their effects on calcium metabolism, hydrochlorothiazide may interfere with tests for parathyroid function (see WARNINGS AND SPECIAL PRECAUTIONS).
Carbamazepine:
Risk of symptomatic hyponatraemia; clinical and biochemical monitoring is required.
Iodine contrast media:
In case of 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 or stimulant laxatives:
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established (see CONTRAINDICATIONS). When pregnancy is planned or confirmed, LOSARTAN COMP BIOTECH should be discontinued.
Medicines affecting the renin-angiotensin system, such as LOSARTAN COMP BIOTECH, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. Women of child-bearing age should ensure effective contraception.
No information is available regarding the use of LOSARTAN COMP BIOTECH tablets during breastfeeding. Hydrochlorothiazide is excreted in human milk. Therefore, the use of LOSARTAN COMP BIOTECH tablets during breastfeeding is not recommended.

DOSAGE AND DIRECTIONS FOR USE:
The usual dose is one LOSARTAN COMP BIOTECH 50/12,5 tablet once daily, with or without food. The maximum dose is LOSARTAN COMP BIOTECH 100/25 once daily. The maximum antihypertensive effect is attained within three weeks after initiation of therapy.
No initial dosage adjustment is necessary for elderly patients.
LOSARTAN COMP BIOTECH is not recommended for patients with history of hepatic or severe renal impairment (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).
LOSARTAN COMP BIOTECH should not be initiated in patients who are intravascular volume-depleted (e.g. those treated with high-dose diuretics).
LOSARTAN COMP BIOTECH may be administered with other antihypertensive agents, particularly calcium channel blockers and beta-blockers.

SIDE EFFECTS:
Losartan potassium:
The following side-effects have been reported:
Immune system disorders
The following have been reported but frequencies are unknown: Angioedema (involving swelling of the face, lips, pharynx and/or tongue) has been reported in patients treated with LOSARTAN COMP BIOTECH.
Blood and the lymphatic system disorders
The following have been reported but frequencies are unknown: Symptomatic anaemia, decreased haemoglobin concentrations, neutropenia
Endocrine disorders
Less frequent: Acute pancreatitis
Nervous system disorders
Frequent: Headache
Less frequent: Dizziness
The following have been reported but frequencies are unknown: Insomnia, migraine, asthenia/ fatigue
Cardiac disorders
Less frequent: Palpitations, tachycardia
Vascular disorders
Less frequent: Hypotension, oedema / swelling
Respiratory, thoracic and mediastinal disorders
Less frequent: Cough, nasal congestion, pharyngitis, sinus disorder, upper respiratory infection, chest pain
Gastrointestinal disorders
Less frequent: Abdominal pain, taste disturbances or complete taste loss
The following have been reported but frequencies are unknown: Diarrhoea, dyspepsia, nausea
Hepato-biliary disorders
The following have been reported but frequencies are unknown: Raised liver enzyme values, severe acute hepatotoxicity, and cholestasis
Skin and subcutaneous tissue disorders
Less frequent: Urticaria, rash, atypical cutaneous lymphoid infiltrates
Musculoskeletal, connective tissue and bone disorders
Less frequent: Back pain, muscle cramps, leg pain, and myalgia
Renal and urinary disorders
The following has been reported but the frequency is unknown: Impaired renal function
Hydrochlorothiazide:
Side effects that have occurred with hydrochlorothiazide are:
Blood and the lymphatic system disorders:
Less frequent: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia.
Immune system disorders
The following have been reported but frequencies are unknown: Purpura, photosensitivity, rash, urticaria, necrotising angiitis (vasculitis), cutaneous vasculitis, fever, respiratory distress including pneumonitis and pulmonary oedema, anaphylactic reactions
Endocrine disorders
Less frequent: Pancreatitis
Metabolism and nutrition disorders
Frequent: Electrolyte imbalance (hyponatraemia), hypochloraemic alkalosis, hypokalaemia
Less frequent: Anorexia, hyperuricaemia
The following have been reported but frequencies are unknown: Hyperglycaemia, glycosuria
Nervous system disorders
The following have been reported but frequencies are unknown: Vertigo, paraesthesia
Eye disorders
The following have been reported but frequencies are unknown: Vision disturbances, xanthopsia
Gastrointestinal disorders
The following have been reported but frequencies are unknown: Gastric irritation, nausea, vomiting, cramping, diarrhoea, constipation, sialoadenitis
Hepato-biliary disorders
The following has been reported but frequencies are unknown: Jaundice (intrahepatic cholestatic jaundice)
Musculoskeletal, connective tissue and bone disorders
The following has been reported but frequencies are unknown: Muscle pain or cramps
Renal and urinary disorders
The following have been reported but frequencies are unknown: Renal dysfunction, interstitial nephritis, renal failure
General disorders:
Less frequent: Dizziness, weakness, restlessness
Losartan Potassium and Hydrochlorothiazide:
The following additional adverse reactions have been reported with losartan-hydrochlorothiazide combination such as LOSARTAN COMP BIOTECH:
Immune system disorders
The following have been reported but frequencies are unknown: Angioedema (involving swelling of the face, lips, pharynx and/or tongue) has been reported in patients treated with LOSARTAN COMP BIOTECH.
Hepato-biliary disorders
Less frequent: Hepatitis

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Losartan Potassium:
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
dysrhythmias. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

IDENTIFICATION:
LOSARTAN COMP BIOTECH 50/12,5: light yellow, round, biconvex, film-coated tablets. Diameter 8,0 – 8,3 mm; thickness 3,3 – 3,8 mm.
LOSARTAN COMP BIOTECH 100/25: light yellow, round, biconvex, film-coated tablets. Diameter 10,0 – 10,2 mm; thickness 4,5 – 5,1 mm.

PRESENTATION:
LOSARTAN COMP BIOTECH 50/12,5 and LOSARTAN COMP BIOTECH 100/25 film-coated tablets are packed into silver Aluminium/ Aluminium blisters or blisters comprising of white ACLAR 3000 film and silver Aluminium foil.
Each blister strip contains 10 tablets.
3 blister strips (30 tablets) are packed into a cardboard carton together with a package insert.

STORAGE INSTRUCTIONS:
Store at or below 30 °C.
Do not remove blisters from the outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:
LOSARTAN COMP BIOTECH 50/12,5: A43/7.1.3/0863
LOSARTAN COMP BIOTECH 100/25: A43/7.1.3/0864

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
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SKEDULERINGSTATUS:
S3

EIENDOMSNAAM EN DOSEERVORM:
LOSARTAN COMP BIOTECH 50/12,5 filmbedekte tablette
LOSARTAN COMP BIOTECH 100/25 filmbedekte tablette

SAMESTELLING:
Elke LOSARTAN COMP BIOTECH 50/12,5 filmbedekte tablet bevat 50 mg kaliumlosartan en 12,5 mg hidrochloortiasied.
Elke LOSARTAN COMP BIOTECH 100/25 filmbedekte tablet bevat 100 mg kaliumlosartan en 25 mg hidrochloortiasied.
Tablet kern: Laktose monohidraat, Magnesiumstearaat, mikrokristallyne sellulose, pregelatineerde stysel, kolloïdale anhidriese silika.
Tablet bedekking: Ferrioksied, hidroksielpropielsellulose, hipromellose, talkum, titaandioksied.
Bevat suiker (Laktose monohidraat).

FARMAKOLOGIESE KLASSIFIKASIE:
A 7.1.3 Ander hipotensiewe middels

FARMAKOLOGIESE WERKING:
Farmakodinamiese eienskappe
LOSARTAN COMP BIOTECH is 'n kombinasie van kaliumlosartan ('n angiotensien II reseptor tipe AT_1 antagonis) en hidrochloortiasied ('n diuretikum).
Losartan:
Losartan is 'n nie-peptied angiotensien II reseptor antagonis met hoë affiniteit en selektiwiteit vir die AT_1 reseptor, sonder om ander hormoonreseptore of ioonkanale wat belangrik is in kardiovaskulêre regulering te bind of te blokkeer. Angiotensien II is 'n kragtige vasokonstriktor, 'n primêre aktiewe hormoon van die renien-angiotensiensisteem. Losartan blokkeer die vasokonstriktor- en aldosteroon-afskeidende effekte van angiotensien II deur die binding van angiotensien II aan die AT_1 reseptor te inhibeer.
Losartan is 'n spesifieke antagonis van die angiotensien-II-reseptor tipe AT_1, dit inhibeer nie AOE (kininase II) die ensiem wat bradikinien afbreek nie. Blokkering van die negatiewe terugvoer van angiotensien II op renienafskeiding tydens toediening van losartan lei tot hoër aktiwiteit van renien in die plasma. 'n 2- tot 3-voudige toename in die konsentrasie van angiotensien II in die plasma volg na toename in die aktiwiteit van renien in die plasma. Die antihipertensiewe aktiwiteit en onderdrukking van die konsentrasie van aldosteroon in die plasma is 'n aanduiding wat die effektiewe blokkasie van die angiotensien-II-reseptor toon. Na staking van losartan neem die aktiwiteit van renien in die plasma en vlakke van angiotensien af.
Hidrochloortiasied:
Hidrochloortiasied is 'n diuretikum en het antihipertensiewe eienskappe; die meganisme van die antihipertensiewe effek van hidrochloortiasied is onbekend. Hidrochloortiasied affekteer gewoonlik nie normale bloeddruk nie. Dit affekteer die distale renale tubulêre meganisme van elektroliet-herabsorpsie. Hidrochloortiasied verhoog die uitskeiding van natrium en chloried in nagenoeg ekwivalente hoeveelhede. Natriurese kan gepaard gaan met 'n mate van verlies van kalium, magnesium en bikarbonaat.
Na orale gebruik, begin diurese binne 2 ure, piek na ongeveer 4 ure en duur ongeveer 6 tot 12 ure.
Kaliumlosartan-Hidrochloortiasied:
Die antihipertensiewe effektiwiteit van losartan en hidrochlortiasied is additief.
Farmakokinetiese eienskappe
Losartan:
Absorpsie
Na orale toediening, is die biobeskikbaarheid ongeveer 33 %. Dit ondergaan eerstedeurgangmetabolisme om 'n aktiewe karboksielsuurmetaboliet, wat 'n sterker farmakologiese aktiwiteit as losartan het, en sommige ander onaktiewe metaboliete.
Verspreiding
Beide losartan en karboksielsuurmetaboliet is meer as of gelyk aan 99 % gebind aan plasmaproteïene. Die verdelingsvolume van losartan is ongeveer 34 liter.
Metabolisme
Ongeveer 14 % van 'n binneaarse of oraal toegediende dosis word na die aktiewe metaboliet omgeskakel. Die gemiddelde piekkonsentrasies van losartan en sy aktiewe metaboliet word onderskeidelik binne 1 en 3 tot 4 uur bereik.
Eliminasie
Losartan word in die urine, en in die ontlasting via die gal, uitgeskei as die onveranderende middel en metaboliet. Na orale dosering word ongeveer 35 % van die dosis uitgeskei in die urine en ongeveer 60 % in die ontlasting. Die terminale halfleeftyd van losartan is 2 uur en dié van die aktiewe metaboliet is 6 tot 9 uur. Nie losartan of sy aktiewe metaboliet kan verwyder word deur hemodialise nie. Die plasmakonsentrasie van losartan in pasiënte met verswakte nierfunksie en 'n kreatinienopruiming van meer as 10 ml/min word nie aangetas nie. In vergelyking met pasiënte met normale nierfunksie, is die AOK vir losartan ongeveer twee maal groter by pasiënte wat hemodialise ontvang.
Hidrochloortiasied:
Hidrochloortiasied word nie gemetaboliseer nie, maar word vinnig deur die niere uitgeskei.
Die plasma halfleeftyd wissel tussen 5,6 en 14,8 ure, na 24 uur observasie. Ten minste 61 % van die orale dosis word binne 24 uur onveranderd uitgeskei. Hidrochloortiasied kruis die plasenta maar nie die bloed-breinskans nie.
Kaliumlosartan-Hidrochloortiasied:
Hidrochloortiasied 12,5 mg verander nie die farmakokinetika van losartan 50 mg of andersom nie.

INDIKASIES:
LOSARTAN COMP BIOTECH word aangedui vir die behandeling van hipertensie by pasiënte wat reeds gestabiliseer is op identiese dosisse van die individuele middels.

KONTRAÏNDIKASIES:
- Sensitiwiteit vir enige van die bestanddele van LOSARTAN COMP BIOTECH.
- 'n Geskiedenis van angio-edeem verwant aan vorige behandeling met AOE inhibeerders of angiotensien reseptor blokkeerders (ARBs): Hierdie pasiënte mag nooit weer hierdie medisyne ontvang nie.
- Oorgeërfde of idiopatiese angio-edeem.
- Hipertrofiese obstruktiewe kardiomiopatie (HOKM).
- Erge nierfunksie-inkorting (kreatinienopruiming minder as 30 ml/min).
- Bilaterale renale arteriestenose.
- Renale arteriestenose by pasiënte met net een nier.
- Aortiese stenose.
- Gelyktydige behandeling met kaliumsparende diuretika, soos spironolaktoon, triamtereen, amiloried.
- Porfirie.
- Tiasiediuretikum in kombinasie met losartan soos in LOSARTAN COMP BIOTECH moet nie aan pasiënte met Addison se siekte gegee word nie. Hierdie behandeling is ook teenaangedui by pasiënte met erge nierontoereikentheid of anurie, en by pasiënte wie hipersensitiwiteit vir ander sulfoonamied-afgeleide medikasie toon.
- Litiumterapie: Gelyktydige behandeling met LOSARTAN COMP BIOTECH mag lei tot toksiese bloedkonsentrasies van litium.
- Swangerskap en laktasie (sien SWANGERSKAP EN LAKTASIE).
- Die veilige en effektiwiteit onder kinders is nog nie vasgestel nie.
- Hipersensitiwiteit vir ander sulfonamied-afgeleide medisyne, as gevolg van die hidrochloortiasied komponent.

WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS:
- Vrouens wat swanger kan raak moet geskikte kontrasepsie verseker.

Indien 'n vrou swanger sou raak terwyl sy LOSARTAN COMP BIOTECH gebruik, moet die behandeling onmiddellik gestaak word en na 'n ander klas van hipertensiewe medikasie verander word (sien KONTRAINDIKASIES EN SWANGERSKAP EN LAKTASIE).

- Erge lewerskade; cholestase en bilière obstruktiewe versteurings.
- Refraktêre hiponatremie.

Hipotensie en elektroliet/vloeistofwanbalans:
Simptomatiese hipotensie mag voorkom by pasiënte wie intravaskulêre volume-uitgeput is (bv. diegene wat met hoë-dosis diuretika behandel word). Hierdie toestande moet reggestel word voor toediening van LOSARTAN COMP BIOTECH, of 'n laer aanvangsdosis moet gebruik word (sien DOSIS EN GEBRUIKSAANWYSINGS).
By pasiënte wie se nierfunksie van die aktiwiteit van die renien-angiotensien-aldosteroonstelsel afhang (bv. pasiënte met ernstige kongestiewe hartversaking), het behandeling met angiotensienomskakelingsensiemremmers met oligurie en/of progressiewe asotemie en (minder dikwels) met akute nierversaking en/of dood gepaard gegaan. Soortgelyke gevolge is waarskynlik met LOSARTAN COMP BIOTECH behandeling.
Aangesien hiperkalemie kan voorkom, moet die konsentrasie van kalium in die serum gemonitor word, veral by bejaarde pasiënte en diegene met verswakte nierfunksie en die gelyktydige gebruik van kaliumsparende diuretika moet oor die algemeen vermy word (sien INTERAKSIES).
Nier- en lewerinkorting:
LOSARTAN COMP BIOTECH word nie aanbeveel vir behandeling van pasiënte met lewerontoereikenddheid of ernstige nierontoereikenddheid nie.
Veranderings in nierfunksie, insluitende nierversaking, is aangemeld weens inhibering van die renien-angiotensiensisteem, hierdie veranderings in die nierfunksie mag omkeerbaar wees wanneer behandeling gestaak word.
Die bloedureum en serumkreatinien kan verhoog wees pasiënte met bilaterale renale arteriestenose of stenose van die arterie na 'n enkele nier gedurende behandeling met LOSARTAN COMP BIOTECH. Hierdie veranderings in nierfunksie mag omkeerbaar wees wanneer behandeling gestaak word.
Metaboliese en endokriene effekte:
Dosisaanpassing van antidiabetiese middels, insluitende insulien, mag nodig wees (sien INTERAKSIES), aangesien tiasied glukosetoleransie kan inkort.
Hidrochloortiasied in LOSARTAN COMP BIOTECH kan urinêre kalsiumuitskeiding verminder en kan 'n intermitterende en effense verhoging van serumkalsium veroorsaak. Gemerkte hipokalsemie kan bewys wees van verborge hiperparatiroïedisme. LOSARTAN COMP BIOTECH moet gestaak word voordat toetse vir paratiroïedfunksie uitgevoer word.
Toenames in cholesterol en trigliseriedvlakke mag geassosieer word met hidrochloortiasied in LOSARTAN COMP BIOTECH. LOSARTAN COMP BIOTECH behandeling mag hiperurisemie en/of jig by sekere pasiënte presipiteer.
Ander:
By pasiënte wat LOSARTAN COMP BIOTECH ontvang, kan sensitiwiteitsreaksies van tiasiede voorkom met of sonder 'n geskiedenis van allergie of brongiale asma. Verergering of aktivering van sistemiese eritematiese lupus is aangemeld met die gebruik van LOSARTAN COMP BIOTECH.
Effekte op die vermoë om te bestuur of masjinerie te gebruik:
Daar is geen data wat daarop dui dat LOSARTAN COMP BIOTECH 'n effek het op die vermoë om te bestuur of masjinerie te gebruik nie. Met die bestuur van voertuie of gebruik van masjinerie moet egter in gedagte gehou word dat duiseligheid of slaperigheid soms voorkom wanneer antihipertensiewe behandeling geneem word, veral tydens die aanvang van behandeling of wanneer die dosis verhoog word.
Belangrike inligting oor sommige van die bestanddele van LOSARTAN COMP BIOTECH:
LOSARTAN COMP BIOTECH bevat laktose. Pasiënte met seldsame oorerflike probleme met galaktose-onverdraagsaamheid, bv. Galaktosemie, die Lapp laktase tekort of glukose-galaktose wanabsorpsie moet nie LOSARTAN COMP BIOTECH neem nie.

INTERAKSIES:
Kaluimlosartan:
Die antihipertensiewe effekte van losartan kan versterk word deur medisyne of ander middels wat bloeddruk verlaag.
Flukonasool kan die konsentrasie van losartan verhoog.
Nie-steroïedale anti-inflammatoriese middels (NSAIMs) kan die antihipertensiewe effek van LOSARTAN COMP BIOTECH antagoniseer.
Gelyktydige gebruik van simpatomimetika kan die antihipertensiewe effek van LOSARTAN COMP BIOTECH verminder.
Kaliumsparende diuretika, kaliumbevattende medikasie of kaliumaanvullings wat saam met LOSARTAN COMP BIOTECH gebruik word, kan tot hiperkalemie lei, aangesien die vermindering van aldosteroonproduksie, geïnduseer deur LOSARTAN COMP BIOTECH, tot verhoogde vlakke van kalium in die serum kan lei.
Litium - sien KONTRAINDIKASIES.
Hidrochloortiasied:
Wanneer dit gelyktydig toegedien word, mag die volgende medikasie met tiasieddiuretika reageer:
Alkohol, dwelms of barbiturate:
Potensiëring van ortostatiese hipotensie mag voorkom.
Anti-diabetiese middels (orale medisyne en insulien):
'n Aanpassing in dosering van die anti-diabetiese medisyne mag nodig wees. Metformien moet met omsigtigheid gebruik word as gevolg van die risiko van melksuursurose wat veroorsaak word deur moontlike funksionele nierversaking wat aan hidrochloortiasied gekoppel is.
Antihipertensiewe medikasie:
Mag 'n additiewe hipotensiewe effek veroorsaak.
Cholestiramien en kolestipolhars:
Absorpsie van hidrochloortiasied word ingekort, enkel dosisse van of cholestiramien of kolestipol bind die hidrochloortiasied en verminder sy absorpsie uit die spysverteringskanaal met tot 85 en 43 persent, onderskeidelik. LOSARTAN COMP BIOTECH moet een uur voor die inname van die hars, geneem word.
Kortikosteroïede of AKTH:
Gelyktydige gebruik mag elektrolietuitputting, veral hipokalemie, vererger.
Litium:
Moet nie saam met diuretika gegee word nie. Diuretiese middels verminder die renale opruiming van litium en dra by tot 'n hoë risiko van litiumtoksisiteit.
Simpatomimetika, soos norepinefrien:
Mag die respons op simpatomimetiese middels verlaag.
Skeletspierverslappers, nie-depolariserende (bv. tubokurarien):
Moontlike verhoogde gevoeligheid vir die spierverslapper.
Nie-steroïedale anti-inflammatoriese medikasie:
Mag die diuretiese, natriuretiese en antihipertensiewe effekte van lus-, kaliumsparende- en tiasieddiuretika verminder.
Medisyne wat gebruik word in die behandeling van jig (probenesied, sulfienpirasoon, allopurinol):
Verhoogde dosisse probenesiede of sulfienpirasoon mag nodig wees. Die hidrochloortiasied in LOSARTAN COMP BIOTECH mag die voorkoms van hipersensitiwiteitsreaksies tetenoor allopurinol verhoog.
Anticholinergiese middels (bv. atropien, biperieden):
Toename van die biobeskikbaarheid by hidrochloortiasied in LOSARTAN COMP BIOTECH deur die vermindering van gastro-intestinale motiliteit en maag leegmaak tempo.
Sitotoksiese middels (bv. siklofosfamied, metotreksaat):
Hidrochloortiasied in LOSARTAN COMP BIOTECH mag die nieruitskeiding van sitotoksiese medisyne verminder en hul myelosuppressiewe effekte verhoog.
Salisilate:
In geval van hoë dosisse salisilate, mag die hidrochloortiasied in LOSARTAN COMP BIOTECH die toksiese effek van die salisilate op die sentrale senuweestelsel verhoog.
Metieldopa:
Daar is berigte van hemolitiese anemie wat voorkom met die gepaardgaande gebruik van hidrochloortiasied soos in LOSARTAN COMP BIOTECH en metieldopa.
Siklosporien:
Gelyktydige behandeling met siklosporien mag die risiko van hiperurisemie en jig-tipe komplikasies verhoog.
Digoksien:
Tiasied-geïnduseerde hipokalemie of hipomagnesemie mag die aanvang van digitalis-geïnduseerde hartdisritmieë bevorder.
Medisyne wat geaffekteer word deur serum kaliumversteurings, soos anti-disritmie, antipsigotika en ander:
Periodiese monitering van serumkalium en EKG word aanbeveel wanneer LOSARTAN COMP BIOTECH gebruik word tesame met medisyne wat geaffekteer word deur serumkaliumversteurings.
Kalsiumsoute:
Hidrochloortiasied soos in LOSARTAN COMP BIOTECH mag serumkalsiumvlakke verhoog as gevolg van verminderde uitskeiding. Serumkalsiumvlakke moet gemonitor word en kalsiumdosering moet dienooreenkomstig aangepas word.
Laboratorium toetsinteraksies:
As gevolg van hul effek op kalsiummetabolisme, mag hidrochloortiasied inmeng met toetse vir paratiroïedfunksie (sien WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
Karbamasepien:
Simptomatiese hiponatremie risiko; kliniese en biochemiese monitering word vereis.
Jodium kontras media:
In geval van dehidrasie, is daar 'n verhoogde risiko van akute nierversaking, veral met hoë dosisse van die jodiumproduk. Pasiënte moet voor die toediening gerehidreer word.
Amfoterisien B (parenterale), kortikosteroïede, ACTH of stimulante lakseermiddels:
Hidrochloortiasied kan 'n elektroliet wanbalans vererger, veral hipokalemie.

SWANGERSKAP EN LAKTASIE:
Veiligheid van gebruik gedurende swangerskap en laktasie is nie bepaal nie (sien KONTRAINDIKASIES). Wanneer swangerskap beplan of bevestig word, moet die gebruik van LOSARTAN COMP BIOTECH gestaak word.
Medisyne wat die renien-angiotensiensisteem affekteer, soos LOSARTAN COMP BIOTECH, mag embrio-toksisiteit, fetale en neonatale morbiditeit en mortaliteit veroorsaak, wanneer dit aan swanger vroue toegedien word. Vrouens wat swanger kan raak moet effektiewe voorbehoeding verseker.
Geen inligting is beskikbaar oor die gebruik van LOSARTAN COMP BIOTECH tablette tydens borsvoeding nie. Hidrochloortiasied word in menslike borsmelk uitgeskei. Daarom word die gebruik van LOSARTAN COMP BIOTECH tablette tydens borsvoeding nie aanbeveel nie.

DOSIS EN GEBRUIKSAANWYSINGS:
Die normale dosis is een LOSARTAN COMP BIOTECH 50/12,5 tablet een maal per dag, met of sonder kos. Die maksimum dosis is LOSARTAN COMP BIOTECH 100/25 een maal per dag. Die maksimum antihipertensiewe effek word binne drie weke na inisiasie van behandeling bereik.
Geen aanpassing in die dosis is nodig vir bejaarde pasiënte nie.
Die gebruik van LOSARTAN COMP BIOTECH word nie aanbeveel vir pasiënte met 'n geskiedenis van lewer- of erge nierversaking nie (sien KONTRAINDIKASIES en WAARSKUWINGS EN SPESIALE VOORSORGMAATREËLS).
LOSARTAN COMP BIOTECH moet nie geïnisieer word by pasiënte wat intravaskulêr volume-uitgeput is nie (bv. dié wat met hoë dosisse diuretika behandel word).
LOSARTAN COMP BIOTECH mag toegedien word tesame met ander antihipertensiewe middels, veral kalsiumkanaalblokkers en beta-blokkers.

NEWE EFFEKTE:
Kaliumlosartan:
Die volgende newe-effekte is aangemeld:
Immuunstelsel afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Angio-edeem (met betrekking tot swelling van die gesig, lippe en/of tong) is aangemeld in pasiënte wat behandel word met LOSARTAN COMP BIOTECH.
Bloed- en limfstelsel afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Simptomatiese anemie, verminderde hemoglobien konsentrasies, neutropenie
Endokriene afwykings
Minder algemeen: Akute pankreatitis
Senuweestelsel afwykings
Algemeen: Hoofpyn
Minder algemeen: Duiseligheid
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Slaaploosheid, migraine, astenie/moegheid
Kardiale afwykings
Minder algemeen: Palpitasies, tagikardie
Vaskulêre afwykings
Minder algemeen: Hipotensie, edeem/swelling
Respiratoriese, torakale en mediastinale afwykings
Minder algemeen: Hoes (droog), toe neus, faringitis, sinusversteuring, infeksie van die boonste lugweg, borspyn.
Gastroïntestinale afwykings
Minder algemeen: Abdominale pyn, smaakversteurings of volledige smaakverlies
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Diarree, dispepsie, naarheid
Hepatobiliêre afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Verhoogde waardes van lewerensieme, ernstige akute lewertoksisiteit, cholestase
Vel- en subkutane weefsel afwykings
Minder algemeen: Urtikarie, veluitslag, atipiese kutane limfinfiltrate
Muskuloskeletale, bindweefsel- en beenafwykings
Minder algemeen: Rugpyn, spierkrampe, beenpyn, mialgie
Nier- en urinêre afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Verswakte nierfunksie
Hidrochloortiasied:
Newe-effekte wat met hidrochloortiasied voorgekom het, is:
Bloed- en limfstelsel afwykings
Minder algemeen: Leukopenie, agranulositose, trombositopenie, aplastiese anemie, hemolitiese anemie.
Immuunstelsel afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Purpura, fotosensitiwiteit, uitslag, urtikaria, nekrotiserende angitis (vaskulitis), kutane vaskulitis, koors, respiratoriese nood, insluitend pneumonitis en pulmonêre edeem, anafilaktiese reaksies
Endokriene afwykings
Minder algemeen: Pankreatitis
Metabolisme en voedings afwykings
Algemeen: Elektrolietwanbalans (hiponatremie), hipochloremiese alkalose, hipokalemie
Minder algemeen: Anorexia, hyperurisemie
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Hiperglukemie, glikosurie
Senuweestelsel afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Vertigo, parestesie
Oog afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Visieversteurings, xantopsie
Gastroïntestinale afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Gastriese irritasie, naarheid, braking, krampe, diarree, hardlywigheid, sialadenitis
Hepatobiliêre afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Geelsug (intrahepatiese cholestatiese geelsug)
Muskuloskeletale, bindweefsel- en beenafwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Spierpyn of krampe
Nier- en urinêre afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Nierdisfunksie, interstisiële nefritis, nierversaking
Algemene afwykings
Minder dikwels: Duiseligheid, swakheid, rusteloosheid
Kaliumlosartan en Hidrochloortiasied:
Die volgende addisionele nadelige reaksies is aangemeld met losartan-hidrochloortiasied-kombinasie soos LOSARTAN COMP BIOTECH:
Immuunstelsel afwykings
Die volgende newe-effekte is aangemeld, maar frekwensies is onbekend: Angio-edeem (met betrekking tot swelling van die gesig, lippe en/of tong) is aangemeld in pasiënte wat behandel word met LOSARTAN COMP BIOTECH.
Hepatobiliêre afwykings
Minder dikwels: Hepatitis

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN:
Kaliumlosartan:
Die mees waarskynlike manifestasie van oordosering sou hipotensie en tagikardie wees; bradikardie kan weens parasimpatiese (vagale) stimulasie voorkom. Indien simptomatiese hipotensie sou voorkom, moet ondersteunende behandeling ingestel word. Nie losartan of die aktiewe metaboliet kan deur hemodialise verwyder word nie.
Hidrochloortiasied:
Die mees algemene tekens en simptome waargeneem is dié wat deur elektrolietuitputting (hipokalemie, hipochloremie, hiponatremie) en dehidrasie weens oormatige diurese, veroorsaak word. Indien digitalis ook toegedien is, mag hipokalemie kardiale aritmieë beklemtoon. Die mate waartoe hidrochloortiasied deur hemodialise verwyder word, is nie bepaal nie.

IDENTIFIKASIE:
LOSARTAN COMP BIOTECH 50/12,5: Liggeel, ronde, bikonvekse, film-bedekte tablette. Diameter 8,0 - 8,3 mm; Dikte 3,3 - 3,8 mm.
LOSARTAN COMP BIOTECH 100/25: Liggeel, ronde, bikonvekse, film-bedekte tablette. Diameter 10,0 - 10,2 mm; Dikte 4,5 - 5,1 mm.

AANBIEDING:
LOSARTAN COMP BIOTECH 50/12,5 en LOSARTAN COMP BIOTECH 100/25 filmbedekte tablette is verpak in silwer aluminium/aluminium stulpverpakkings of stulpverpakkings wat bestaan uit 'n wit ACLAR 3000 film en silwer aluminium foelie.
Elke stulpstrook bevat 10 tablette.
Drie stulpstroke (30 tablette) word verpak in 'n karton saam met 'n voubiljet.

BERGINGSINSTRUKSIES:
Bêre teen of benede 30 °C.
Hou stulpstroke in die karton tot benodig vir gebruik.
HOU BUITE BEREIK VAN KINDERS.

REGISTRASIENOMMERS:
LOSARTAN COMP BIOTECH 50/12,5: A43/7.1.3/0863
LOSARTAN COMP BIOTECH 100/25: A43/7.1.3/0864

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