Losartan Potassium Hydrochlorothiazide

Myotan-H

50 mg / 12.5 mg Film-Coated Tablet
Angiotensin II Receptor Blocker (ARB)/ Diuretic

℞

FORMULATION:
Each film-coated tablet contains:
Losartan Potassium ..... 50 mg
Hydrochlorothiazide ..... 12.5 mg

CHEMISTRY:
Losartan Potassium, a non-peptide molecule, is chemically described as 2-butyl-4-chloro-1-[p-(0-1H-tetrazole-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt.
Hydrochlorothiazide, is a diuretic drug of the thiazide class that acts by inhibiting the kidney's ability to retain water.

PRODUCT DESCRIPTION:
Yellow, circular, biconvex film-coated tablets.

LIST OF EXCIPIENTS:
Pregelatinised Starch NF, Lactose Monohydrate NF, Microcrystalline Cellulose NF (Avicel PH 101), Purified Water USP, Croscamellose Sodium NF, Magnesium Stearate NF, Opadry 03FS20076 Yellow (In-house).

INDICATIONS:
For the treatment of essential hypertension in patients whose blood pressure is not adequately controlled on hydrochlorothiazide or losartan monotherapy.

DOSAGE AND ADMINISTRATION:
Losartan Potassium + Hydrochlorothiazide may be administered with other Antihypertensive (Angiotensin II Receptor Blocker/Diuretic Combination) agents.
Losartan Potassium + Hydrochlorothiazide should be swallowed with a glass of water.
Losartan Potassium + Hydrochlorothiazide may be administered with or without food.

Hypertension
Losartan and hydrochlorothiazide is not for use as initial therapy, but in patients whose blood pressure is not adequately controlled by losartan potassium or hydrochlorothiazide alone.
Dose titration with the individual components (losartan and hydrochlorothiazide) is recommended.
When clinically appropriate direct change from monotherapy to the fixed combination may be considered in patients whose blood pressure is not adequately controlled.
The usual maintenance dose is one tablet of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-Coated tablets (Losartan 50 mg/HCTZ 12.5 mg) once daily. For patients who do not respond adequately to Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-Coated tablets, the dosage may be increased to maximum 2 tablets daily of Losartan Potassium/Hydrochlorothiazide 50 mg/12.5 mg Film-Coated tablets or one tablet of Losartan Potassium/Hydrochlorothiazide 100 mg/25 mg Film-Coated tablets (Losartan 100 mg/HCTZ 25 mg) once daily. In general the Antihypertensive (Angiotensin II Receptor Blocker/Diuretic Combination) effect is attained within three to four weeks after initiation of therapy.
Use in patints with renal impairment and haemodialysis patients
No initial dosage adjustment is necessary in patients with moderate renal impairment (i.e. creatinine clearance 30-50 ml/min). Losartan and hydrochlorothiazide tablets are not recommended for haemodialysis patients. Losartan/HCTZ tablets must not be used in patients with severe renal impairment (i.e. creatinine clearance <30 ml/min).
Use in patients with hepatic impairment
Losartan/HCTZ is contraindicated in patients with severe hepatic impairment.
Use in the elderly
Dosage adjustment is not usually necessary for the elderly.
Use in children and adolescents (< 18 years)
There is no experience in children and adolescents. Therefore, losartan/hydrochlorothiazide should not be administered to children and adolescents.

CONTRAINDICATIONS:
-Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients.
-Therapy resistant hypokalaemia or hypercalcaemia
-Severe hepatic impairment; cholestasis and biliary obstructive disorders
- Refractory hyponatraemia
- Symptomatic hyperuricaemia/gout
- 2nd and 3rd trimester of pregnancy
-Severe renal impairment (i.e. creatinine clearance <30 mL/min)
- Anuria
-The concomitant use of Losartan Potassium / Hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m2).

WARNINGS:
Safety information on risk of Non-Melanoma Skin Cancer with prolonged use of Hydrochlorothiazide
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism of NMSC.

Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC.

PRECAUTIONS:
-Hypersensitivity to losartan, sulphonamide-derived substances (as hydrochlorothiazide) or to any of the excipients.
- Therapy resistant hypokalaemia or hypercalcaemia.
- Severe hepatic impairment: Cholestasis and biliary obstructive disorders.
- Refractory hyponatraemia
- Symptomatic hyperrucaemia
- 2nd and 3rd trimester of pregnancy.
- Severe renal impairment (i.e. creatinine clearance <30 ml/min).
- Anuria
- Do not co-administer aliskiren with Losartan Potassium + Hydrochlorothiazide in patients with diabetes.

PREGNANCY:
Angiotensin II Receptor Antagonists (AIIRAs):
The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the 2nd and 3rd trimester or pregnancy.
Epidemiological evidence regarding the risk of tetratogenicity following exposure to Angiotensin Converting Enzyme (ACE) inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative Antihypertensive (Angiotensin II Receptor Blocker/Diuretic Combination) treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately and, if appropriate, alternative therapy should be started.
Exposure to AIIRA therapy during the second and third trimester is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation and neonatal toxicity (renal failure, hypotension, hyperkalemia).
Should exposure to AIIRAs have occured 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.
Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

ADVERSE DRUG REACTIONS:
Adverse effects of losartan have been reported to be usually mild and transient, and include dizziness, headache, and dose-related orthostatic hypotension. Hypotension may occur particularly in patients with volume depletion (for example those who have received highdose diuretics). Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzyme values may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. Losartan appears less likely than ACE inhibitors to cause cough. Other adverse effects that have been reported with angiotensin II receptor antagonists include respiratory-tract disorders, back pain, gastrointestinal disturbances, fatigue, and neutropenia. Rhabdomyolysis has been reported rarely.

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

Losartan

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	anaemia, Henoch-Schönlein purpura, ecchymosis, haemolysis	uncommon
	thrombocytopenia	not known
Cardiac disorders	hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, palpitation, arrhythmias (atrial fibrillations, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation)	uncommon
Ear and labyrinth disorders	vertigo, tinnitus	uncommon
Eye disorders	blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity	uncommon
Gastrointestinal disorders	abdominal pain, nausea, diarrhea, dyspepsia	common
	constipation, dental pain, dry mouth, flatulence, gastritis, vomiting, obstipation	uncommon
	pancreatitis	not known
General disorders and administration site conditions	asthenia, fatigue, chest pain	common
	facial oedema, oedema, fever	uncommon
	flu-like symptoms, malaise	not known
Hepatobiliary disorders	liver function abnormalities	not known
Immune system disorders	hypersensitivity: anaphylactic reactions, angioedema including swelling of the larynx 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 medicinal products, including ACE inhibitors;	rare
Metabolism and nutrition disorders	anorexia, gout	uncommon
Musculoskeletal and connective tissue disorders	muscle cramp, back pain, leg pain, myalgia	common
	arm pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, coxalgia, fibromyalgia, muscle weakness	uncommon
	rhabdomyolysis	not known
Nervous system disorders	headache, dizziness	common
	nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope	uncommon
	dysgeusia	not known
Psychiatric disorders	insomnia	common
	anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment	uncommon
Renal and urinary disorders	renal impairment, renal failure	common
	nocturia, urinary frequency, urinary tract infection	uncommon
Reproductive system and breast disorders	decreased libido, erectile dysfunction/impotence	uncommon
Respiratory, thoracic and mediastinal disorders	cough, upper respiratory infection, nasal congestion, sinusitis, sinus disorder	common
	pharyngeal discomfort, pharyngitis, laryngitis, dyspnoea, bronchitis, epistaxis, rhinitis, respiratory congestion	uncommon
Skin and subcutaneous tissue disorders	alopecia, dermatitis, dry skin, erythema, flushing, photosensitivity, pruritus, rash, urticaria, sweating	uncommon
Vascular disorders	vasculitis	uncommon
	dose-related orthostatic effects	not known
Investigations	hyperkalaemia, mild reduction of haematocrit and haemoglobin, hypoglycaemia	common
	mild increase in urea and creatinine serum levels	uncommon
	increase in hepatic enzymes and bilirubin	very rare
	hyponatraemia	non known

Hydrochlorothiazide

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia	uncommon
Immune system disorders	Anaphylactic reaction	rare
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia	uncommon
Psychiatric disorders	Insomnia	uncommon
Nervous system disorders	Cephalalgia	common
Eye disorders	Transient blurred vision, xanthopsia	uncommon
Vascular disorders	Necrotizing angiitis (vasculitis, cutaneous vasculitis)	uncommon
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis and pulmonary oedema	uncommon
Gastrointestinal disorders	Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation	uncommon
Hepato-biliary disorders	Icterus (intrahepatic cholestatis), pancreatitis	uncommon
Skin and subcutaneous tissue disorders	Photosensitivity, urticaria, toxic epidermal necrolysis	uncommon
	cutaneous lupus erythematosus	not known
Musculoskeletal and connective tissue disorders	Muscle cramps	uncommon
Renal and urinary disorders	Glycosuria, interstitial nephritis, renal dysfunction, renal failure	uncommon
General disorders and administration site conditions	Fever, dizziness	uncommon

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed.

DRUG INTERACTION:
The Antihypertensive (Angiotensin II Receptor Blocker/Diuretic Combination) effects of losartan may be potentiated by drugs or other agents that lower blood pressure. An additive hyperkalaemic effect is possible with potassium supplements, potassium-sparing diuretics, or other drugs that can cause hyperkalaemia; losartan and potassium-sparing diuretics should not generally be given together. NSAIDs should be used with caution in patients taking losartan as the risk of renal impairment may be increased, particularly in those who are inadequately hydrated; use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) may also attenuate
the hypotensive effect of losartan. Losartan and some other angiotensin II receptor antagonists are metabolised by cytochrome P450 isoenzymes and interactions may occur with drugs that affect these enzymes.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Angiotensin II antagonists and diuretics.
Losartan Potassium/Hydrochlorothiazide
The components of Losartan Potassium/Hydrochlorothiazide 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.
The antihypertensive effect of Losartan Potassium/Hydrochlorothiazide is sustained for a 24-hour period. In clinical studies of at least one year's duration, the antihypertensive effect was maintained with continued therapy. Despite the significant decrease in blood pressure, administration of Losartan Potassium /Hydrochlorothiazide had no clinically significant effect on heart rate. In clinical trials, after 12 weeks of therapy with losartan 50 mg/hydrochlorothiazide 12.5 mg, trough sitting diastolic blood pressure was reduced by an average of up to 13.2 mmHg.
Losartan Potassium/Hydrochlorothiazide is effective in reducing blood pressure in males and females, blacks and non-blacks and in younger (<65 years) and older (>65 years) patients and is effective in all degrees of hypertension.

PHARMACOKINETICS:
Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial firstpass metabolism resulting in a systemic bioavailability of about 33%. It is metabolised to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively,
after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.
Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma t½ has been observed to vary between 5.6 and 14.8 hrs. At least 61% of the oral dose is eliminated unchanged within 24 hrs.

OVERDOSE AND TREATMENT:
No specific information is available on the treatment of overdosage with Losartan Potassium Hydrochlorothiazide (Myotan-H). Treatment is symptomatic and supportive. Therapy with Losartan Potassium + Hydrochlorothiazide 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 in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic vagal stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.
Neither losartan nor the active metabolite can be removed hemodialysis.
Hydrochlorothiazide
the most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.
The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov. Seek medical attention immediately at the first sign of any adverse drug reaction.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C. Protect from light.
Keep out of reach of children

AVAILABILITY:
Alu/Alu Blister Pack x 10's (Box of 30's and 100's)

DRP-6574
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