For the use only of a Registered Medical Practitioner or a Hospital.

Dichlor

Chlorthalidone Tablets USP

DESCRIPTION
Chlorthalidone is a monosulfonamyl diuretic. It is a benzothiadiazine (thiazide) -related diuretic with a long duration of action. Chemically, chlorthalidone is 2 -Chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl) benzene sulfonamide.Its molecular formula is $C_{14}H_{11}ClN_2O_4S$ and its molecular weight is 338.8

COMPOSITION
Dichlor-12.5
Each tablet contains:
Chlorthalidone USP 12.5 mg
Dichlor-25
Each tablet contains:
Chlorthalidone USP 25 mg
Dichlor-50
Each tablet contains:
Chlorthalidone USP 50 mg

PHARMACOLOGY
Chlorthalidone is a long-acting oral diuretic with antihypertensive activity.
The drug produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the distal convoluted tubule of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow.
In hypertensive individuals, chlorthalidone gently reduces blood pressure. Although the mechanism of action of chlorthalidone is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.
It increases bicarbonate, phosphate and magnesium excretion (mainly proximal tubule) and sodium, chloride and potassium excretion (mainly distal tubule); increased potassium excretion is because of enhanced (flow dependent) potassium secretion and is greater on a high sodium intake. By contrast calcium excretion (distal tubule) is decreased and this can be useful in hypercalciuria and renal stones.
Diuretic action of chlorthalidone commences a mean of 2.6 hours after dosing and continues for up to 72 hours.
Like the thiazide diuretics, chlorthalidone produces dose-related reductions in serum potassium levels, elevations in serum uric acid and blood glucose and it can lead to decreased sodium and chloride levels.
Like most thiazide diuretics, it is an inhibitor of carbonic anhydrase and is 70 times as potent as hydrochlorothiazide in inhibiting carbonic anhydrase.

PHARMACOKINETICS
Oral chlorthalidone is absorbed from the gastrointestinal tract (about 65%). Though very little chlorthalidone in blood is free, most is bound to red cell carbonic anhydrase (98%), rather than plasma protein. Concentration in red cells is 50 - 80 times the concentrations in plasma or serum.
Metabolites have not been identified. Metabolism and hepatic excretion into bile constitute a minor pathway of elimination.
50 - 65% of an oral dose is excreted unchanged in the urine. Upto 10% can be recovered in feces, indicating biliary or intestinal elimination. The mean plasma half life of chlorthalidone is about 40 to 60 hours.

INDICATIONS
Chlorthalidone is indicated for:
- Treatment of arterial hypertension, essential or nephrogenic or isolated systolic.
- Treatment of stable, chronic heart failure of mild to moderate degree (NYHA functional class II or III).
- Treatment of oedema.

CONTRAINDICATIONS
Chlorthalidone is contraindicated in:
- Patients with known hypersensitivity to chlorthalidone or other sulfonamide derived drugs.
- Anuria.
- Severe hepatic or renal failure (creatinine clearance <30ml/min).
- Refractory hypokalaemia, hyponatraemia and hypercalcaemia.
- Symptomatic hyperuricaemia (history of gout or uric acid calculi).
- Hypertension during pregnancy.
- Untreated Addison's disease.
- Concomitant lithium therapy.

WARNINGS
Renal disease
Chlorthalidone should be used with caution in severe renal disease. In patients with renal disease, chlorthalidone or related drugs may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Hepatic disease
Chlorthalidone should be used with caution in patients with impaired hepatic function or progressive liver disease, because minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Others:
Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics, which are structurally related to chlorthalidone. However, systemic lupus erythematosus has not been reported following chlorthalidone administration.

PRECAUTIONS
General:
Hypokalemia and other electrolyte abnormalities, including hyponatremia, hypomagnesemia and hypochloremic alkalosis, are common in patients receiving chlorthalidone. These abnormalities are dose-related but may occur even at the lowest marketed doses of chlorthalidone.
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients taking chlorthalidone should be observed for clinical signs of electrolyte imbalance, including dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, palpitations and gastrointestinal disturbances, such as nausea and vomiting. Patients with cirrhosis are sensitive to diuretic induced changes in volume and electrolyte status. Hence volume depletion, potassium depletion and/or hyponatremia can precipitate hepatic encephalopathy in such patients.
Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity.
If necessary, chlorthalidone may be combined with potassium supplements or a potassium sparing diuretic (e.g. triamterene). If hypokalaemia is accompanied by clinical signs (e.g. muscular weakness, paresis and ECG alteration), chlorthalidone should be discontinued. Combined treatment consisting of chlorthalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather: appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In cases of actual salt depletion, appropriate replacement is the therapy of choice.
Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (e.g. nausea, debility, progressive disorientation and apathy) following thiazide treatment.
For nephrotic syndrome, chlorthalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.
Uric acid:
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving chlorthalidone.
Other:
Increases in serum glucose may occur and latent diabetes mellitus may become manifest during chlorthalidone therapy.
Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides or low density lipoprotein cholesterol were reported in patients during long-term treatment with thiazide and thiazide like diuretics. The clinical relevance of these findings is a matter for debate.
The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretics be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.
Chlorthalidone should not be used as a first line drug for long term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).
As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.
Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.
Effects on ability to drive and use machines
Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.
Usage in pregnancy and lactation
Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia and foetal and neonatal jaundice associated with the use of thiazide diuretics.
Chlorthalidone passes into the breast milk; mothers taking chlorthalidone should refrain from breast feeding their infants.
Usage in paediatrics
Safety and effectiveness in the paediatric population have not been established.

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Usage in geriatrics
While clinical experience generally has not revealed age-related differences in response to the drug, care should be taken in dosage selection of chlorthalidone. Because of the greater frequency of decreased hepatic, renal and/or cardiac function and of concomitant disease and drug therapy in geriatric patients, patients in this age group should receive initial dosages of the drug in the lower end of the usual range.

DRUG INTERACTIONS
Chlorthalidone may add to or potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE inhibitors).
The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma rennin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.
The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, $ß_2$-agonists, amphotericin and carbenoxolone.
Insulin requirements in diabetic patients may be increased, decreased or unchanged. Higher dosage of oral hypoglycemic agents may be required.
Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias.
Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indomethacin) may reduce the diuretic and antihypertensive activity of chlorthalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.
Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.
Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.
Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.
Lithium renal clearance is reduced by chlorthalidone, increasing the risk of lithium toxicity.
Patients should also be cautioned that taking alcohol can increase the chance of dizziness occurring.
Diuretic induced volume depletion can potentiate aminoglycoside nephrotoxicity.
Chlorthalidone can reduce prothrombin activity. Thiazide derivatives may potentiate the bone marrow suppression caused by cancer chemotherapy (e.g. neutropenia).

ADVERSE DRUG REACTIONS
Gastrointestinal: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis.
Central Nervous System: Dizziness, vertigo, paresthesias, headache, xanthopsia.
Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, eosinophilia.
Dermatologic - Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis vasculitis (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis).
Cardiovascular: Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Very rare cardiac arrhythmias may occur.
Electrolytes and metabolic disorders: Hypokalaemia, hyponatraemia, hypomagnesaemia, hyperglycaemia, hyperuricemia, rise in blood lipids, glycosuria and hypochloraemic alkalosis
Other adverse reactions: Muscle spasm, weakness, restlessness, impotence. Very rarely idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis may occur.
Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

OVERDOSAGE
Symptoms of acute overdosage include nausea, weakness, somnolence, hypovolaemia, hypotension, dizziness and disturbances of electrolyte balance associated with cardiac arrhythmias and muscle spasms. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established.
There is no specific antidote to chlorthalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

DOSAGE AND ADMINISTRATION
Dose of chlorthalidone should be individualised according to patient's requirements and response. If chlorthalidone is added to the regimen of a patient stabilized on a potent hypotensive agent, the dosage of the hypotensive agent should initially be reduced to avoid the possibility of severe hypotension.
Hypertension
Monotherapy - For the management of hypertension, an initial adult chlorthalidone dosage of 12.5 - 25mg daily has been recommended. This is sufficient to produce the maximum hypotensive effect in most patients. If the decrease in blood pressure proves inadequate with 25mg/day, then the dose can be increased to 50mg/day. If a further reduction in blood pressure is required, additional antihypertensive therapy may be added to the dosage regime. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.
Combination therapy - When combination therapy is required in the management of hypertension, dosage can be adjusted first by administering each drug separately. If it is determined that the optimum maintenance dosage corresponds to the ratio in a commercial combination preparation, the fixed combination may be used. Whenever dosage adjustment is necessary, each drug then can be administered separately.
Stable, chronic heart failure (NYHA: functional class II/III)
The recommended starting dose is 25 to 50mg/day, in severe cases it may be increased up to 100 to 200mg/day. The usual maintenance dose is the lowest effective dose e.g. 25 to 50mg/day either daily or every other day. If the response proves inadequate, digitalis or an ACE inhibitor or both may be added.
Edema
The usual initial adult dosage of chlorthalidone for the management of edema is 50 - 100mg daily in a single dose after breakfast. Alternatively, therapy may be initiated at a dosage of 100mg every other day or 3 times a week. Some patients may require dosages of 150 - 200mg daily or every other day. Dosages greater than 200mg daily do not produce a greater response. In edematous patients, reduction of dosage to a lower maintenance level may be possible after several days or when nonedematous weight is attained.
Elderly patients and patients with renal impairment
The lowest effective dose of chlorthalidone is also recommended for patients with mild renal insufficiency and for elderly patients.
In elderly patients, the elimination of chlorthalidone is slower than in healthy young adults, although absorption is the same. Therefore, a reduction in the recommended adult dosage may be needed. Close medical observation is indicated when treating patients of advanced age with chlorthalidone.
Chlorthalidone and the thiazide diuretics lose their diuretic effect when the creatinine clearance is <30ml/min.

LIST OF EXCIPIENTS
Microcrystalline Cellulose USP-NF, Pregelatinised Starch USP-NF, D & C Yellow No.10 (Quinoline Yellow Lake) IH, Sodium Starch Glycollate USP-NF, Colloidal Silicon Dioxide USP-NF, Stearic Acid USP-NF, Purified Water USP.

STORAGE
Store below 30ºC, in a dry place
KEEP OUT OF REACH OF CHILDREN

PRESENTATION
Blister strip of 10 Tablets

Date of publication: Sept. 2016

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