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

ARKAMIN H

1. Generic Name

Clonidine Hydrochloride and Hydrochlorothiazide Tablets

2. Qualitative and quantitative Composition:

Each uncoated tablet contains:

Clonidine Hydrochloride I.P……..100 µg

Hydrochlorothiazide I.P. ……20 mg

Excipients……..…q.s.

Colour: Quinoline Yellow WS

The excipients used are Lactose, Maize Starch, Colour Quinoline Yellow WS, Methyl Paraben, Magnesium Stearate, and Talcum.

3. Dosage form and strength

Dosage form: Uncoated tablet

Strength: 100 µg and 20 mg

4. Clinical particulars

4.1. Therapeutic indication

Indicated for the treatment of hypertension.

4.2. Posology and method of administration

Dosage: As directed by the Physician.

4.3. Contraindications

Clonidine hydrochloride should not be used in patients with known hypersensitivity to the active ingredient or other components of the product, and in patients with severe Bradyarrhythmia resulting from either sick sinus syndrome or AV block of 2nd or 3rd degree.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to section 4.4 Special Warnings and Precautions for Use) the use of the product is contraindicated.

- Hypersensitivity to this product or to other sulfonamide-derived drugs.
- Anuria.

4.4. Special warnings and precautions for use

Clonidine Hydrochloride

Caution should be exercised in patients with Raynaud's disease or other peripheral vascular disease. As with all drugs used in hypertension Clonidine hydrochloride should be used with caution in patients with cerebrovascular or coronary insufficiency.

Clonidine hydrochloride should also be used with caution in patients with mild to moderate Bradyarrhythmia such as low sinus rhythm, and with polyneuropathy or constipation.

Patients with a known history of depression should be carefully supervised while under longterm treatment with Clonidine hydrochloride as there have been occasional reports of further depressive episodes during oral treatment in such patients.

As with other antihypertensive drugs, treatment with Clonidine hydrochloride should be monitored particularly carefully in patients with heart failure.

In hypertension caused by phaeochromocytoma no therapeutic effect of Clonidine hydrochloride can be expected.

Clonidine, the active ingredient of Clonidine hydrochloride, and its metabolites are extensively excreted in the urine. Dosage must be adjusted to the individual antihypertensive response, which can show high variability in patients with renal insufficiency; careful monitoring is required. Since only a minimal amount of clonidine is removed during routine haemodialysis there is no need to give supplemental clonidine following dialysis.

Sudden withdrawal of Clonidine hydrochloride, particularly in those patients receiving high doses, may result in rebound hypertension. Cases of agitation, restlessness, palpitations, nervousness, tremor, headache and abdominal symptoms have also been reported. Patients should be instructed not to discontinue therapy without consulting their physician. When discontinuing therapy, the physician should reduce the dose gradually. However, if withdrawal symptoms should nevertheless occur, these can usually be treated with reintroduction of clonidine or with alpha and beta adrenoceptor blocking agents.

If Clonidine hydrochloride is being given concurrently with a beta-blocker, Clonidine hydrochloride should not be discontinued until several days after the withdrawal of the betablocker.

Patients who wear contact lenses should be warned that treatment with Clonidine hydrochloride may cause decreased lacrimation.

This product contains 36.1 mg of lactose monohydrate per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The use and the safety of clonidine in children and adolescents has little supporting evidence in randomized controlled trials and therefore cannot be recommended for use in this population.

Serious adverse events, including sudden death, have been reported in concomitant use with methylphenidate. The safety of using methylphenidate in combination with clonidine has not been systematically evaluated.

Hydrochlorothiazide

Warnings: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Thiazides may add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics.

Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure

glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Precautions

General

All patients receiving diuretic therapy should be observed for evidence of fluid or electrolyte imbalance: namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia.

Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium sparing diuretics or potassium supplements such as foods with a high potassium content. Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

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 actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazides.

In diabetic patient’s dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyper glycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

4.5. Drugs interactions

Clonidine Hydrochloride

The reduction in blood pressure induced by clonidine can be further potentiated by concurrent administration of other hypotensive agents. This can be of therapeutic use in the case of other antihypertensive agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists and ACE-inhibitors, but the effect of alpha1-blockers is unpredictable.

The antihypertensive effect of clonidine may be reduced or abolished and orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

Substances which raise blood pressure or induce a sodium ion (Na+) and water retaining effect such as non-steroidal anti-inflammatory agents can reduce the therapeutic effect of clonidine.

Substances with alpha2-receptor blocking properties, such as mirtazapine, may abolish the alpha2-receptor mediated effects of clonidine in a dose-dependent manner.

Concomitant administration of substances with a negative chronotropic or dromotropic effect such as beta-receptor blockers or digitalis glycosides can cause or potentiate bradycardic rhythm disturbances.

It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders.

Based on observations in patients in a state of alcoholic delirium it has been suggested that high intravenous doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol. Causal relationship and relevance for antihypertensive treatment have not been established.

The effects of centrally depressant substances or alcohol can be potentiated by clonidine.

Hydrochlorothiazide

Drug Interactions: When given concurrently the following drugs may interact with thiazide diuretics. Alcohol, Barbiturates, or Narcotics: Potentiation of orthostatic hypotension may occur. Antidiabetic Drugs (Oral Agents and Insulin): Dosage adjustment of the antidiabetic drug may be required. Other Antihypertensive Drugs: 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%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia. Pressor Amines (e.g., Norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use. Skeletal Muscle Relaxants, Nondepolarizing (e.g., Tubocurarine): Possible increased responsiveness to the muscle relaxant. Lithium: Generally, should not be given with diuretics.

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with hydrochlorothiazide. Non-Steroidal Anti-Inflammatory Drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics.

Therefore, Reference ID: 3001472 when hydrochlorothiazide and non-steroidal antiinflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. Drug/Laboratory Test Interactions: Thiazides should be discontinued before carrying out tests for parathyroid function. Carcinogenesis, Mutagenesis, Impairment of Fertility: Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of

Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Clonidine Hydrochloride

Pregnancy

There are limited amount of data from the use of clonidine in pregnant women. This product should only be used in pregnancy if considered essential by the physician. Careful monitoring of mother and child is recommended.

Clonidine passes the placental barrier and may lower the heart rate of the foetus. Post-partum a transient rise in blood pressure in the newborn cannot be excluded.

There is no adequate experience regarding the long-term effects of prenatal exposure.

During pregnancy the oral forms of clonidine should be preferred. Intravenous injection of clonidine should be avoided.

Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Lactation

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of Clonidine hydrochloride is therefore not recommended during breastfeeding.

Fertility

No clinical studies on the effect on human fertility have been conducted with clonidine.

Non-clinical studies with clonidine indicate no direct or indirect harmful effects with respect

to the fertility index.

Hydrochlorothiazide

Pregnancy

Teratogenic Effects

Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers

Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother.

Pediatric Use

There are no well controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients.

4.7. Effects on ability to drive and use machines

Clonidine Hydrochloride

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with Clonidine hydrochloride. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Hydrochlorothiazide

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

4.8. Undesirable effects

Clonidine Hydrochloride

Most adverse effects are mild and tend to diminish with continued therapy.

Adverse events have been ranked under headings of frequency using the following convention:

Very common	≥ 1/10
Common	≥ 1/100, <1/10
Uncommon	≥1/1000, <1/100
Rare	≥1/10000, <1/1000
Very rare	<1/10000
Not known	Cannot be estimated from the available data
Endocrine disorders:	
Gynaecomastia	rare

Psychiatric disorders:	
Confusional state	not known
Delusional perception	uncommon
Depression	common
Hallucination	uncommon
Libido decreased	not known
Nightmare	uncommon
Sleep disorder	common
Nervous system disorders:	
Dizziness	very common
Headache	common
Paraesthesia	uncommon
Sedation	very common
Eye disorders:	
Accommodation disorder	not known
Lacrimation decreased	rare
Cardiac disorders:	
Atrioventricular block	rare
Bradyarrhythmia	not known
Sinus bradycardia	uncommon
Vascular disorders:	
Orthostatic hypotension	very common
Raynaud's phenomenon	uncommon

Respiratory, thoracic and mediastinal disorders:	
Nasal dryness	rare
Gastrointestinal disorders:	
Colonic pseudo-obstruction	rare
Constipation	common
Dry mouth	very common
Nausea	common
Salivary gland pain	common
Vomiting	common
Skin and subcutaneous tissue disorders:	
Alopecia	rare
Pruritus	uncommon
Rash	uncommon
Urticaria	uncommon
Reproductive system and breast disorders:	
Erectile dysfunction	common
General disorders and administration site conditions:	
Fatigue	common
Malaise	uncommon
Investigations:	
Blood glucose increased	rare

There are occasional reports of fluid retention during initial stages of oral treatment. This is usually transitory and can be corrected by the addition of a diuretic.

Occasional reports of abnormal liver function tests and two cases of hepatitis have also been reported.

Hydrochlorothiazide

The following adverse reactions have been reported and, within each category, are listed in order of decreasing severity. Body as a Whole: Weakness. Cardiovascular: Hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs). Digestive: Pancreatitis, jaundice (intrahepatic cholestatic jaundice), diarrhea, vomiting, sialadenitis, cramping, constipation, gastric irritation, nausea, anorexia. Hematologic: Aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity: Anaphylactic reactions, necrotizing angiitis (vasculitis and cutaneous vasculitis), respiratory distress including pneumonitis and pulmonary edema, photosensitivity, fever, urticaria, rash, purpura.

Metabolic: Electrolyte imbalance, hyperglycemia, glycosuria, hyperuricemia.

Musculoskeletal: Muscle spasm.

Nervous System/Psychiatric: Vertigo, paresthesias, dizziness, headache, restlessness.

Renal: Renal failure, renal dysfunction, interstitial nephritis.

Skin: Erythema multiforme including Stevens- Johnson Syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia.

Special Senses: Transient blurred vision, xanthopsia.

Urogenital: Impotence. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose

Clonidine Hydrochloride

Symptoms:

Manifestations of intoxication are due to a generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia, somnolence including coma and respiratory depression including apnoea. Paradoxical hypertension caused by stimulation of peripheral alpha1-receptors may occur. Transient hypertension may be seen if the total dose is over 10 mg.

Treatment:

There is no specific antidote for clonidine overdose. Administration of activated charcoal should be performed where appropriate.

Supportive care may include atropine sulfate for symptomatic bradycardia, and intravenous fluids and/or inotropic sympathomimetic agents for hypotension. Severe persistent hypertension may require correction with alpha-adrenoceptor blocking drugs.

Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression.

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. In the event of overdosage, symptomatic and supportive measures should be employed. Emesis should be induced or gastric lavage performed. Correct dehydration, electrolyte imbalance, hepatic coma and hypotension by established procedures. If required, give oxygen or artificial respiration for respiratory impairment. The degree to which hydro chlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydro chlorothiazide is greater than 10 g/kg in the mouse and rat.

5. Pharmacological properties

5.1. Mechanism of Action

Clonidine Hydrochloride

Clonidine hydrochloride has been shown to have both central and peripheral sites of action. With long-term treatment Clonidine hydrochloride reduces the responsiveness of peripheral vessels to vasoconstrictor and vasodilator substances and to sympathetic nerve stimulation. Early in treatment, however, blood pressure reduction is associated with a central reduction of sympathetic outflow and increased vagal tone.

Hydrochlorothiazide

Hydrochlorothiazide blocks the reabsorption of sodium and chloride ions, and it thereby increases the quantity of sodium traversing the distal tubule and the volume of water excreted. A portion of the additional sodium presented to the distal tubule is exchanged there for potassium and hydrogen ions. With continued use of hydrochlorothiazide and depletion of sodium, compensatory mechanisms tend to increase this exchange and may produce excessive loss of potassium, hydrogen and chloride ions. Hydrochlorothiazide also decreases the excretion of calcium and uric acid, may increase the excretion of iodide and may reduce glomerular filtration rate. Metabolic toxicities associated with excessive electrolyte changes caused by hydrochlorothiazide have been shown to be dose-related.

5.2. Pharmacodynamic properties

Clonidine Hydrochloride

Clinically, there may be reduced venous return and slight bradycardia resulting in reduced cardiac output. Although initially peripheral resistance may be unchanged, it tends to be reduced as treatment continues. There is no interference with myocardial contractility. Studies have shown that cardiovascular reflexes, as shown by the lack of postural hypotension and exercise hypotension, are preserved.

The efficacy of clonidine in the treatment of hypertension has been investigated in five clinical studies in paediatric patients. The efficacy data confirms the properties of clonidine in reduction of systolic and diastolic blood pressure. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of clonidine for hypertensive children.

The efficacy of clonidine has also been investigated in a few clinical studies with paediatric patients with ADHD, Tourette syndrome and stuttering. The efficacy of clonidine in these conditions has not been demonstrated.

There were also two small paediatric studies in migraine, neither of which demonstrated efficacy. In the paediatric studies the most frequent adverse events were drowsiness, dry

mouth, headache, dizziness and insomnia. These adverse events might have serious impact on daily functioning in paediatric patients.

Overall, the safety and efficacy of clonidine in children and adolescents have not been established.

Hydrochlorothiazide

Acute antihypertensive effects of thiazides are thought to result from a reduction in blood volume and cardiac output, secondary to a natriuretic effect, although a direct vasodilatory mechanism has also been proposed. With chronic administration, plasma volume returns toward normal, but peripheral vascular resistance is decreased. The exact mechanism of the antihypertensive effect of hydrochlorothiazide is not known.

5.3. Pharmacokinetic properties

Clonidine Hydrochloride

The pharmacokinetics of clonidine is dose-proportional in the range of 100 to 600 μg. The absolute bioavailability of clonidine on oral administration is 70% to 80%. Peak plasma clonidine levels are attained in approximately 1 to 3 hours.

Following intravenous administration, clonidine displays biphasic disposition with a distribution half-life of about 20 minutes and an elimination half-life ranging from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Clonidine crosses the placental barrier. It has been shown to cross the blood-brain barrier in rats.

Following oral administration about 40% to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Neither food nor the race of the patient influences the pharmacokinetics of clonidine.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/mL in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.

Hydrochlorothiazide

Hydrochlorothiazide is well absorbed (65% to 75%) following oral administration. Absorption of hydrochlorothiazide is reduced in patients with congestive heart failure. Peak plasma concentrations are observed within 1 to 5 hours of dosing, and range from 70 to 490 ng/mL following oral doses of 12.5 to 100 mg. Plasma concentrations are linearly related to the administered dose. Concentrations of hydrochlorothiazide are 1.6 to 1.8 times higher in whole blood than in plasma. Binding to serum proteins has been reported to be approximately 40% to 68%. The plasma elimination half-life has been reported to be 6 to 15 hours. Hydrochlorothiazide is eliminated primarily by renal pathways. Following oral doses of 12.5 to 100 mg, 55% to 77% of the administered dose appears in urine and greater than 95% of the absorbed dose is excreted in urine as unchanged drug. In patients with renal disease, plasma concentrations of hydrochlorothiazide are increased and the elimination half-life is prolonged. When administered with food, its bioavailability is reduced by 10%, the maximum plasma concentration is reduced by 20%, and the time to maximum concentration increases from 1.6 to 2.9 hours.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Clonidine hydrochloride

<u>Toxicology</u>

In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the start of clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Chronic dietary administration of clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dosed, respectively, at up to 46 or 70 times the maximum recommended daily human dose as mg/kg (9 or 6 times the MRDHD on a mg/m^2 basis). There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male or female rats was unaffected by clonidine doses as high as 150 μg/kg (approximately 3 times MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 μg/kg (10 to 40 times the oral MRDHD on a mg/kg basis; 2 to 8 times the MRDHD on a mg/m basis).

Hydrochlorothiazide

Toxicity

Recognized side effects that have been associated with the use of hydrochlorothiazide include hypokalemia with resultant muscle cramps, cardiac arrhythmia, hyperglycemia, and hyperlipidemia. A variety of hypersensitivity reactions have also been reported. Electrolyte imbalances, in particular hypokalemia and hypomagnesemia, may be involved in increased incidences of sudden death in patients with pre-existing electrocardiographic abnormalities.

Results of the large Multiple Risk Factor Intervention Trial, a 10-year, multicenter study of factors involved in heart disease, indicated that high dose hydrochlorothiazide therapy (100 mg/day) was associated with greater incidences of sudden death in patients with both high blood pressure and electrocardiographic abnormalities. The involvement of hypokalemia and hypomagnesemia in this observation remains a point of controversy. One electrolyte change that occurs with long-term hydrochlorothiazide therapy in humans is increased calcium ion retention; hypercalcemia occasionally results.

A related finding is an association of hydrochlorothiazide treatment with hyperparathyroidism. It has been suggested that thiazides cause a primary hyperparathyroidism, and the reduced calcium ion excretion and increased potassium ion loss seen with these diuretics may, at least in part, be secondary to increased parathyroid hormone secretion. Gave 20 dogs daily doses of 50-200 mg hydrochlorothiazide for up to 9 months; all dogs administered hydrochlorothiazide had enlarged and hyperactive parathyroid glands. Thiazide diuretics also induce a transient increase in serum cholesterol and triglyceride levels, raising the possibility that long-term treatment may contribute to atherosclerosis, although the importance of these transient increases has been disputed.

Hypertensive individuals receiving 50 mg hydrochlorothiazide per day for 4 weeks had increased concentrations of total plasma cholesterol, of high density, low density, and very

low density lipoproteins, and of triglycerides. Increased plasma levels of fasting glucose and insulin were also observed dosed Syrian golden hamsters daily with 1,2, or 4 mg/kg hydrochlorothiazide by gavage for 6 months. At 6 months, they observed increased total cholesterol, triglyceride, and high density lipoprotein cholesterol levels.

Glucose intolerance is a frequently encountered side effect of long-term thiazide therapy and may be associated with hypokalaemia, but the mechanism for this effect is not understood. Other diuretics have similar effects on glucose tolerance.

Immunologic reactions to hydrochlorothiazide therapy were reported, including cases of severe allergic pneumonitis, a photo allergic dermatitis resembling subacute cutaneous lupus erythematosus and several types of hematologic dyscrasias. Neutropenia was reported in several patients with a pattern of onset which suggested a toxic depression of the bone marrow.

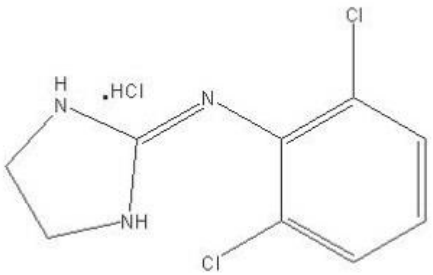
On the other hand, thrombocytopenia also was reported with hydrochlorothiazide therapy and with other thiazides and appears to be immunologically mediated.

In one person, a specific IgM antibody was identified as an antiplatelet factor associated with hydrochlorothiazide-induced thrombocytopenia. The LO50 of orally administered hydrochlorothiazide to an unspecified strain of mice was 3,080 mg/kg. Fed diets containing 0 or 1,000 ppm hydrochlorothiazide to groups of 24 male and 24 female rats for 2 years. The incidence and severity of chronic progressive nephropathy was increased in the dosed rats, as were lesions secondary to chronic renal disease and polyarthritis and mural thrombosis. No increases in neoplastic lesions were seen in dosed rats.

7. Description

Clonidine Hydrochloride:

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The empirical formula of Clonidine hydrochloride is ($C_9H_9Cl_2N_3$,HCl) and its molecular weight is 266.6. Its structural formula is:

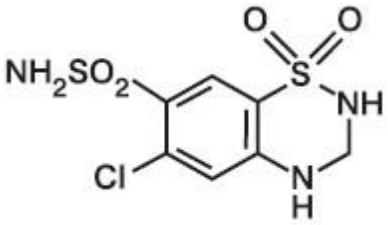


Clonidine hydrochloride is a white or almost white crystalline powder. It is freely soluble in water and in ethanol (95%); slightly soluble in chloroform; practically insoluble in ether.

Hydrochlorothiazide

Hydrochlorothiazide is a white or almost white, crystalline powder; odourless with a molecular weight of 297.74. It is soluble in acetone; sparingly soluble in ethanol (95%); very slightly soluble in water. It dissolves in dilute solutions of alkali hydroxides.

Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



Clonidine Hydrochloride and Hydrochlorothiazide Tablets are Yellow colour, flat, round flat faced bevel edge (FFBE) shaped, uncoated tablet having break line on upper side, ARKAMIN-H embossed on the lower side. The excipients used are Lactose, Maize Starch, Colour Quinoline Yellow WS, Methyl Paraben, Magnesium Stearate and Talcum.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

ARKAMIN H is available in blister strips of 10 tablets each.

8.4. Storage and handing instructions

Store in a cool, dry and dark place. Keep all medicines out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Manufactured in India by:

Uni Medicolabs 21-22 Pharmacity, Selaqui, Dehradun, Uttarakhand

11. Details of permission or licence number with date

Mfg. Licence No.: 65/UA/2015 Issued on: 15.10.2018

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