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

ARKAMIN 150

1. Generic Name

Clonidine Hydrochloride Tablets I.P. 150 mcg

2. Qualitative and quantitative Composition:

Each uncoated tablet contains:

Clonidine Hydrochloride I.P……150 mcg

Excipients……..……q.s.

The Excipient used are Lactose, Maize Starch, Glycerin, Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate, and Talc.

3. Dosage form and strength

Dosage form: Uncoated tablet

Strength: 150 mcg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for

- All grades of essential hypertension.
- Renal hypertension.

4.2 Posology and method of administration

Posology

Adults: The dose of clonidine hydrochloride tablets must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration.

Initial Dose: 200 mcg to 300 mcg per day in divided doses.

Maintenance Dose: Increase the daily dosage at weekly intervals until desired control of blood pressure is achieved. Taking the larger portion of the oral daily dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. Dosage adjustment by small increments is desirable up to a maximum recommended dose of 900 micrograms per day.

In impaired renal and hepatic function, the half-life is prolonged and the dosage regimen should be monitored carefully. In Patients with renal impairment may benefit from a lower initial dose. Patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

Method of administration

Clonidine hydrochloride tablets to be taken orally with or without food. Swallow tablets whole. Do not crush or chew the tablets because this will increase the rate of clonidine release.

4.3 Contraindications

Clonidine hydrochloride should not be used in patients with known hypersensitivity to the active ingredient, clonidine hydrochloride, and in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or AV block of second or third degree.

In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated.

4.4 Special warnings and precautions for use

Special care should be exercised in treating patients who have a history of depression or who have advanced cerebrovascular disease. Reduction of blood pressure in the latter circumstances may itself cause mental changes. Concurrent administration of tricyclic antidepressants may require adjustment of ARKAMIN dosage.

Although a transient rise in blood sugar has been noted occasionally in humans treated with ARKAMIN, which may be due to a pharmacologic alpha-adrenomimetic effect of the drug, no case of induced diabetes mellitus due to ARKAMIN has been reported. Patients with clinical diabetes mellitus should be watched for a possible increase in their requirements of anti-diabetic therapy.

ARKAMIN should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, with disorders of cerebral or peripheral perfusion, polyneuropathy, and constipation.

No therapeutic effect of ARKAMIN can be expected in the treatment of hypertension caused by phaeochromocytoma.

Since ARKAMIN, and its metabolites are extensively excreted in the urine, careful adjustment of dosage is required in patients with renal insufficiency.

As with other anti-hypertensives, treatment with ARKAMIN should be monitored particularly carefully in patients with heart failure or severe coronary heart disease.

Termination of oral therapy should be gradual (e.g. over more than 7 days).

Sudden cessation of antihypertensive therapy is known to be associated in some instances with rebound hypertension which in some cases may be severe. This may occur with ARKAMIN particularly in patients receiving more than the maximum recommended dose of 900 micrograms per day.

Following sudden discontinuation of ARKAMIN after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported.

An excessive rise in blood pressure following discontinuation of ARKAMIN therapy can be reversed by intravenous phentolamine.

If long-term treatment with a β-blocker needs to be interrupted, the β-blocker should be gradually phased out first, then clonidine.

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

<u>Anaesthesia</u>

Abrupt withdrawal of ARKAMIN is undesirable. Limited evidence suggests that it is unnecessary to withdraw ARKAMIN before anaesthesia and that maintenance of therapy is preferable to abrupt withdrawal. In the peri-operative period ARKAMIN can, where necessary, be administered parenterally until oral therapy is resumed.

Where therapy with ARKAMIN is to be suspended before operation, withdrawal should be gradual (i.e. over more than 7 days) and monitored by regular observation of blood pressure.

Use in the elderly

No data available

Paediatric use

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

In particular, when clonidine is used off-label concomitantly with methylphenidate in children with ADHD, serious adverse reactions, including death, have been observed. Therefore, clonidine in this combination is not recommended.

Effects on laboratory tests

No data available

4.5 Drug interactions

If the patient is on antihypertensive therapy, care should be taken as even a small dose of clonidine may further lower blood pressure and necessitate adjustment of the antihypertensive regime.

When ARKAMIN is used as an antihypertensive agent additional clonidine for the prophylaxis of migraine or the alleviation of symptoms in menopausal flushing should not be prescribed. ARKAMIN may potentiate the effects of alcohol, sedatives, hypnotics or other centrally active substances.

Although retinal, lens or corneal damage have not been detected with clonidine therapy, follow up procedures, such as ophthalmoscopy, are recommended.

Substances which raise blood pressure or induce a sodium and water retaining effect such as nonsteroidal anti-inflammatory drugs can reduce the therapeutic effect of clonidine.

Substances with α2-adrenergic receptor blocking properties, such as phentolamine, may abolish the α2-adrenergic receptor mediated effects of clonidine in a dose-dependent way.

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

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

The antihypertensive effect of clonidine may be reduced or abolished and orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with α-receptor blocking effects.

Based on observations in patients in a state of delirium alcoholicum, 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.

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

Effects on fertility

Clinical studies on the effect of clonidine on human fertility have not been conducted.

Clonidine had no effect on fertility in male or female rats when administered orally at doses up to 0.15 mg/kg/day (35% higher than the maximum recommended total daily dose of clonidine in humans, based on body surface area).

Use in pregnancy (Category B3)

Clonidine hydrochloride has not shown teratogenic potential when tested in rats, but in some circumstances the incidence of embryonic and perinatal deaths was increased with doses comparable to those used clinically for antihypertensive therapy.

There are limited data from the use of clonidine in pregnant women, but the experience with clonidine hydrochloride since marketing does not include any positive evidence of adverse effect on the foetus. Since this experience cannot exclude such an effect, clonidine hydrochloride should be used during pregnancy only when the benefit clearly justifies the possible risk to the foetus.

Clonidine passes the placental barrier, and may lower the heart rate of the foetus. There is no adequate experience regarding the long-term effects of prenatal exposure.

Clonidine hydrochloride may also induce transitory elevation of blood glucose and impairment of glucose tolerance. Children born to mothers treated with clonidine hydrochloride during pregnancy should be specifically examined for changes in glucose metabolism.

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

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

Postpartum a transient rise in blood pressure in the newborn cannot be excluded.

Use in lactation

Clonidine is excreted in human milk. As the effect on the new-born is not known, infants born to mothers being treated with Clonidine Hydrochloride should not be breast fed.

4.7 Effects on ability to drive and use machines

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. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The following adverse events (regardless of causality) and incidences are based on a review of 22 clinical studies comprising 640 patients treated with clonidine hydrochloride.

The corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System Organ Class	Very Common	Common	Uncommon	Rare	Not Known
Endocrine disorders:				Gynaecomastia	
Psychiatric disorders:		Depression, sleep disorder	Delusional perception, hallucination, nightmare		Confusional state, libido decreased
Nervous system disorders:	Dizziness, sedation	Headache	Paraesthesia		
Eye disorder:				Lacrimation decreased	Accommodation disorder
Cardiac disorders:			Sinus bradycardia	Atrioventricular block	Bradyarrhythmia
Vascular disorders:	Orthostatic hypotension		Raynaud's phenomenon		
Respiratory, thoracic and mediastinal disorders:				Nasal dryness	
Gastrointestinal disorders:	Dry mouth	Constipation, nausea, salivary gland pain, vomiting		Colonic pseudo-obstruction	
Skin and subcutaneous tissue disorders:			Pruritus, rash, urticaria	Alopecia	
Reproductive system and breast disorders:		Erectile dysfunction			
General disorders and administration site conditions:		Fatigue	Malaise		
Investigations:				Blood glucose increased	

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

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9 Overdose

Symptoms

The most important features of clonidine over dosage are likely to be bradycardia, sedation, respiratory depression including apnoea and somnolence including coma. Blood pressure response may be variable and may vary from severe hypotension (due to central sympathetic inhibition and vagal stimulation) to severe hypertension (due to direct alpha agonist activity). Treatment must therefore be appropriate to the clinical features (i.v. atropine followed by a pressor amine if necessary in patients with hypotension or an alpha blocker such as phentolamine for patients with hypertension). Other features which may be seen include weakness, vomiting, diminished or absent reflexes, skin pallor, hypothermia, cardiac arryhthmias and constricted pupils with poor reaction to light.

Management

General supportive measures with regular checks of pulse, B.P., ECG, blood sugar and body temperature should be undertaken. The blood pressure should be monitored carefully for 48 hours following the overdosage, as a later hypertensive phase may be associated with declining blood levels of clonidine.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of Action

The hypotensive effect of clonidine hydrochloride is produced mostly by its central effect or reducing sympathetic drive. In this respect clonidine hydrochloride differs from previously used anti-hypertensives. clonidine hydrochloride neither depletes major catecholamine stores, nor acts as a ganglion blocking agent. The specific and different mode of action of clonidine hydrochloride leads to benefits such as reduced incidence of postural hypotension and only rarely an effect on libido.

The central action of clonidine hydrochloride is ascribed mainly to an action on the bulbar structures of the central nervous system, particularly the sympathetic cardio-accelerator and constrictor mechanisms. This central action leads to decreased sympathetic outflow. Peripheral effects of clonidine hydrochloride include both vasodilatation and vasoconstriction in various vascular beds, and alpha- and possible beta-adrenomimetic effects. A transient rise in blood sugar occurs following large doses of clonidine hydrochloride. In addition, a small transient pressor effect (5-10 mm Hg systolic blood pressure) lasting approximately five minutes may occur following intravenous use. These effects reflect the alpha-adrenomimetic action of clonidine hydrochloride. The peripheral effects of clonidine hydrochloride generally require isolated organ type preparations for their demonstration, as in the intact animal or man, the central action predominates.

5.2 Pharmacokinetic properties

Absorption and distribution

The pharmacokinetics of clonidine is dose-proportional in the range of 75-300 micrograms. Clonidine, the active ingredient of clonidine hydrochloride is well absorbed from the gastrointestinal tract and undergoes a minor first pass effect. Peak plasma concentrations are reached within 1-3 hours after oral administration. The duration of action varies from 6-12 hours, the duration of action being longer in the milder hypertensives. The plasma protein binding is 30-40%.

Metabolism and excretion

The terminal elimination half-life of clonidine has been found to range from 9-26 hours in patients with normal renal function. With impaired renal function it has been reported to increase to 18-48 hours.

The metabolic pathway of clonidine involves cleavage of the imidazolidine ring and the hydroxylation of the phenyl ring. Five metabolites have been identified in man and include para-hydroxy-clonidine and dichlorophenylguanidine.

Two thirds of an administered dose is excreted in the urine (about half of which is unchanged clonidine hydrochloride) and the remainder is excreted in the faeces.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/mL in patients with normal renal function. The hypotensive effect is attenuated or decreases with plasma concentrations above 2.0 ng/mL.

Given intravenously clonidine hydrochloride is effective within five minutes, has a maximum hypotensive action within 20 to 30 minutes, and the effect lasts for several hours. Following intramuscular administration, clonidine hydrochloride is effective within 5 to 10 minutes. The maximum hypotensive effect is reached after 75 minutes and the duration of action is approximately 5 hours.

In a study designed to evaluate the pharmacokinetics of clonidine following administration of clonidine hydrochloride controlled release tablets (formulation not registered in Australia) in 30 patients (13 white patients, 6 black patients and 11 Hispanic patients), the pharmacokinetics was found to be similar between subjects from different racial groups.

The pharmacokinetics of clonidine is not influenced by food.

6 Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Genotoxicity

Comprehensive investigations have not been performed to assess the potential genotoxic effects of clonidine. Clonidine showed no activity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

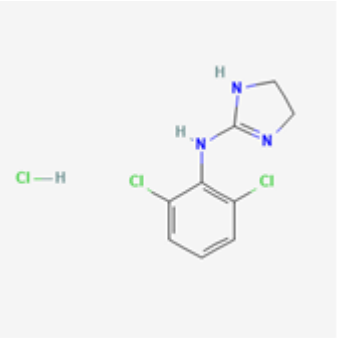
Carcinogenicity

The carcinogenic potential of clonidine has not been assessed in an adequate range of studies. In rats, dietary administration of clonidine at doses up to 1.2 mg/kg/day (males) or 1.5 mg/kg/day (females) did not cause carcinogenic effects. These doses are 10-14 times the maximum recommended human daily dose of clonidine, based on body surface area

7 Description

Clonidine Hydrochloride:

Clonidine Hydrochloride is N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine;hydrochloride. The empirical formula is $C_9H_{10}Cl_3N_3$ and its molecular weight is 266.6 g/mol. The structural formula is:



Arkamin 150:

Clonidine Hydrochloride Tablets are White coloured, flat, round shaped uncoated tablet having breakline on one side and plain on the other side. The Excipient used are Lactose, Maize Starch, Glycerin, Colloidal Silicon Dioxide (Aerosil), Magnesium Stearate, and Talc.

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 150 is available in pack of 30 tablets.

8.4 Storage and handing instructions

Store Below 30°C.

Keep the medicine 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

Uni Medicolabs

Plot No. 21-22, Pharmacity,

Selaqui, Dehradun-248011,

Uttarakhand, India.

11 Details of permission or licence number with date

Mfg. Licence No.: 65/UA/2015, Issued on: Aug-2021.

12. Date of revision

SEP-2025

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ARKAMIN 150 mcg/SEP-2025/03/PI