

CLONIDINE HCl INJECTION
150 microgram/ 1 mL ampoule
New Zealand Data Sheet



CLONIDINE HYDROCHLORIDE INJECTION

1 PRODUCT NAME

Clonidine HCl Injection

Clonidine Hydrochloride 150 microgram/1mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clonidine Hydrochloride 150 microgram/1mL

For the full list of excipients, see section 6.1 *List of excipients*.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of hypertensive crises, slow parental administration is especially suitable due to the rapid onset of action.

4.2 Dose and method of administration

Subcutaneous or intramuscular injection of Clonidine HCl Injection should only be administered to patients in a lying position.

A dosage of 0.2 mcg/kg/minute is recommended for i.v. infusion. The rate of infusion should not exceed 0.5 mcg/kg/minute to avoid transient blood pressure increase. No more than 0.15mg should be used per infusion.

If necessary, ampoules can be administered parenterally up to four times a day.

Clonidine HCl Injection contains 0.154 mmol sodium (3.5 mg) per ampoule.

Renal insufficiency

Dosage must be adjusted:

- according to the individual antihypertensive response which can show high variability in patients with renal insufficiency
- according to the degree of renal impairment.

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.

4.3 Contraindications

Clonidine HCl Injection 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 (please refer to *Precautions*) the use of the product is contraindicated.

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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 Clonidine HCl Injection dosage.

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

Clonidine HCl Injection 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 Clonidine HCl Injection can be expected in the treatment of hypertension caused by pheochromocytoma.

Since CLONIDINE HYDROCHLORIDE Injection, and its metabolites are extensively excreted in the urine, careful adjustment of dosage is required in patients with renal insufficiency (see section 4.2 *Dose and method of administration; Renal insufficiency*).

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

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 particularity in patients receiving more than the maximum recommended dose of 900 micrograms per day.

Following sudden discontinuation of Clonidine HCl Injection after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with Clonidine HCl Injection, the physician should reduce the dosage gradually over 2-4 days.

An excessive rise in blood pressure following discontinuation of *Clonidine HCl Injection* therapy can be reversed by intravenous phentolamine (see *Interactions with other medicines*).

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 *Clonidine HCl Injection* may cause decreased lacrimation.

Paediatric population

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.

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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.

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.

4.5 Interaction with other medicines and other forms of interaction

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 CLONIDINE HYDROCHLORIDE 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. CLONIDINE HYDROCHLORIDE 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 α_2 -adrenergic receptor blocking properties, such as phentolamine, may abolish the α_2 -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. Studies with combined administration of clonidine and β -blockers have shown that if treatment is to be discontinued, the dose of the β -blockers must always be slowly diminished first followed by the clonidine.

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.

Anaesthesia

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

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Where therapy with Clonidine HCl Injection 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.

4.6 Fertility, pregnancy and lactation

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 (see Effects on Fertility).

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

Breast-feeding

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.

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).

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 HCl Injection. 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.

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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.

Endocrine disorders:

≥0.01% and <0.1% gynaecomastia

Psychiatric disorders:

≥1% and <10% depression, sleep disorder

≥0.1% and <1% delusional perception, hallucination, nightmare

Not known confusional state, libido decreased

Nervous system disorders:

≥10% dizziness, sedation

≥1% and <10% headache

≥0.1% and <1% paraesthesia

Eye disorder:

≥0.01% and <0.1% lacrimation decreased

Not known accommodation disorder

Cardiac disorders:

≥0.1% and <1% sinus bradycardia

≥0.01% and <0.1% atrioventricular block

Not known bradyarrhythmia

Vascular disorders:

≥10% orthostatic hypotension

≥0.1% and <1% Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:

≥0.01% and <0.1% nasal dryness

Gastrointestinal disorders:

≥10% dry mouth

≥1% and <10% constipation, nausea, salivary gland pain, vomiting

≥0.01% and <0.1% colonic pseudo-obstruction

Skin and subcutaneous tissue disorders:

≥0.1% and <1% pruritus, rash, urticaria

≥0.01% and <0.1% alopecia

Reproductive system and breast disorders:

≥1% and <10% erectile dysfunction

General disorders and administration site conditions:

≥1% and <10% fatigue

≥0.1% and <1% malaise

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Investigations:

≥0.01% and <0.1%

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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

The most important features of clonidine overdose 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 arrhythmias 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 overdose, as a later hypertensive phase may be associated with declining blood levels of clonidine.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

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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.

Active Ingredient

Active ingredient: clonidine hydrochloride

Chemical name: 2,6-dichloro-N-2-imidazolidinylidene-benzenamine hydrochloride

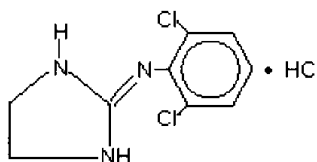
Molecular formula: $C_9H_9N_3Cl_2.HCl$

Molecular weight: 266.56

CAS number: 4205-91-8

Laboratory designation: ST 155

Structural formula:



Description

CLONIDINE HYDROCHLORIDE is a white or almost white, crystalline powder. It is soluble in ethanol, slightly soluble in chloroform and practically insoluble in ether. One gram is soluble in 13 mL of water (20 °C).

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 HCl Injection 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%.

Biotransformation and elimination

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.

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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 HCl Injection 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 HCl Injection 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.

5.3 Preclinical safety data

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Sodium chloride

Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

Not applicable.

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

60 months.

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6.4 Special precautions for storage

This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.

Store below 25°C. Protect from light.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Type 1 clear glass 1mL ampoules packed in outer cardboard carton.

Pack size: 5 ampoules and 10 ampoules.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Use in one patient on one occasion only. Discard any unused residue.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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10 DATE OF REVISION OF THE TEXT

13th April 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Update to shelf life