AUSTRALIAN PRODUCT INFORMATION – CATAPRES® 100 CLONIDINE HYDROCHLORIDE TABLETS

1. NAME OF THE MEDICINE

clonidine hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CATAPRES 100 tablets contain 100 micrograms of clonidine hydrochloride.

Each CATAPRESS 100 tablet contains 36.1 mg of lactose monohydrate.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

CATAPRES 100 tablets are white, round, flat tablets with bevelled edges, one side marked with “01C / break line / 01C”. Each tablet contains 100 micrograms of clonidine hydrochloride.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oral: All grades of essential hypertension.

Renal hypertension.

The prophylactic management of migraine or recurrent vascular headaches which occur in adult patients with a frequency of more than once a month and are not adequately relieved by appropriate therapy for the acute attack. Alleviation of symptoms due to localised vasodilatation in menopausal flushing.

4.2 Dose and method of administration

The dosage recommendations are as follows:

Antihypertensive - initially 50-100 micrograms two to three times daily adjusted in small increments according to the patient's individual blood pressure response. If adequate control is not achieved with a daily dose of 600 micrograms of CATAPRES alone, additional therapy should be considered. Since the hypotensive effect of CATAPRES is dose dependent, it is usual to titrate the dose to satisfy the requirements for each patient. In impaired renal and hepatic function the half-life is prolonged and the dosage regime should be monitored carefully.

*Migraine prophylaxi*s - initially 25 micrograms morning and evening. If necessary, after two weeks, this may be increased to 50 micrograms twice daily, then to a total daily dose of 150 micrograms. If the frequency of attacks is significantly reduced, consideration may be given to gradually ceasing therapy as remission may be sustained in a proportion of patients. Duration of treatment will depend upon the frequency and severity of attacks.

Menopausal flushing - initially 25 micrograms morning and evening. If after two weeks there has been no remission, increase to 50 micrograms twice daily. If necessary this may be increased to a total daily dose of

150 micrograms. Duration of treatment will depend upon the frequency and severity of attacks but long-term efficacy (longer than 8 weeks) in the treatment of menopausal flushing has not been established.

Renal impairment

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

CATAPRES 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 (see Section 4.4 Special warnings and precautions for use) 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 CATAPRES dosage.

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

CATAPRES 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 CATAPRES can be expected in the treatment of hypertension caused by phaeochromocytoma.

Since CATAPRES 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).

As with other anti-hypertensives, treatment with CATAPRES 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 CATAPRES particularly in patients receiving more than the maximum recommended dose of 900 micrograms per day.

Following sudden discontinuation of CATAPRES 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 CATAPRES therapy can be reversed by intravenous phentolamine (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 CATAPRES may cause decreased lacrimation.

CATAPRES 100 tablets contain 308.7 mg of lactose monohydrate per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

Anaesthesia

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

Where therapy with CATAPRES 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.

Menopausal Flushing

The efficacy of clonidine in the treatment of menopausal flushing has only been demonstrated in the first year after onset of symptoms.

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 Interactions 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 CATAPRES 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. CATAPRES 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 bradycardiac 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 Fertility, pregnancy and lactation

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 (see Section 4.6 Fertility, Pregnancy and Lactation).

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 newborn is not known, infants born to mothers being treated with CATAPRES 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 CATAPRES. 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 Adverse effects (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 registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms

The most important features of clonidine overdosage are likely to be bradycardia and 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 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

Antihypertensive effect

CATAPRES is predominantly an antihypertensive agent whose mechanism of action appears to be central alpha2 adrenergic stimulation, as demonstrated in animal studies. This results in the inhibition of bulbar sympathetic cardioaccelerator and sympathetic vasoconstrictor centres, thereby causing a decrease in sympathetic outflow from the brain. There is an increase in vagal activity which produces a decrease in heart rate. There is also an increase in baroreceptor activity. Additionally CATAPRES stimulates peripheral alpha1 adrenergic receptors. This is reflected by a small transient pressor effect (5-10 mmHg systolic blood pressure) following parenteral use. A transient rise in blood sugar may also occur following large doses of CATAPRES. The peripheral effects of CATAPRES generally require isolated organ type preparations for their demonstration, as in the intact animal or man, the central action predominates.

Use in migraine prophylaxis and menopausal flushing

Smaller doses of clonidine hydrochloride may be used for migraine prophylaxis and the alleviation of symptoms in menopausal flushing. The mechanism of action appears to be modification of the response of peripheral blood vessels to vasoconstrictor and vasodilator stimuli including noradrenaline, isoprenaline and angiotensin.

Clinical trails

No data available

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 CATAPRES, 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 CATAPRES) 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, CATAPRES 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, CATAPRES 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 CATAPRES 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

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

CATAPRES 100 tablets contain the excipients maize starch, lactose monohydrate, calcium hydrogen phosphate, colloidal anhydrous silica, povidone and stearic acid.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of

this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

CATAPRES 100 tablets should be stored below 30°C.

6.5 Nature and contents of container

Blister Pack PVC/PVDC

CATAPRES 100 tablets are available in blister packs containing 100 tablets.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

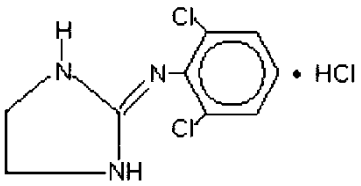
Chemical name: 2,6-dichloro-N-2-imidazolidinylidene-benzenamine hydrochloride

Molecular formula: C9H9N3Cl2.HCl

Molecular weight: 266.56

Laboratory designation: ST 155

Structural formula:



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).

CAS number

4205-91-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Clinect Pty Ltd

120-132 Atlantic Drive

Keysborough, VIC 3173

Australia

Free call Australia: 1800 899 005

9. DATE OF FIRST APPROVAL

8 November 1984

10. DATE OF REVISION

09 August 2023

Summary Table of Changes

Section Changed	Summary of New Information
3	Update to remove the symbol embossing on the tablet