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# NEW ZEALAND DATA SHEET

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## 1. CATAPRES

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CATAPRES 150 mcg tablets

CATAPRES 150 mcg/mL solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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CATAPRES 150 mcg tablets

One tablet contains 150 mcg clonidine hydrochloride

Excipient with known effect: One tablet contains 36.05 mg lactose monohydrate

CATAPRES 150 mcg/mL solution for injection

Each 1 mL ampoule contains 150 mcg clonidine hydrochloride

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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CATAPRES 150 mcg tablets

150 mcg scored white compressed, impressed with the symbol 15C/15C on one side and the Boehringer Ingelheim symbol on the other side

CATAPRES 150 mcg/mL solution for injection

150 mcg/mL clear, colourless solution

## 4. CLINICAL PARTICULARS

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### 4.1 Therapeutic indications

#### Oral

CATAPRES is indicated in the treatment of hypertension. CATAPRES may be employed alone or concomitantly with other antihypertensive agents.

#### Parenteral

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

### 4.2 Dosage and method of administration

#### Tablets

It is recommended to slowly titrate the oral dose of CATAPRES to satisfy the requirements of individual patients.

### *Initially*

Commence on 75 mcg (half a tablet) at night. At successive consultations (2-4 week intervals) the daily dose should be increased by half a tablet (75 mcg), until adequate blood pressure control is attained. The total daily dose is recommended to be taken once daily at night if the optimal dose is 1 tablet or less. If the total daily dose is greater than 1 tablet then dosage should be taken twice daily in evenly divided doses. Where the dosage is uneven the larger dose should be taken at night. Usually doses above 600 mcg per day do not result in a further marked drop in blood pressure.

### *Maintenance*

Most patients with mild to moderate hypertension will be controlled on a dose of 150-450 mcg daily.

In more severe cases, higher doses of up to 900 mcg daily have been utilised on a 300 mcg (2 tablets), twice to three times daily dosage regimen.

### Injection

CATAPRES ampoules when administered subcutaneously or intramuscularly should be given with the patient in a recumbent 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.

CATAPRES ampoules contain less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially 'sodium-free'.

### Renal insufficiency

Dosage must be adjusted

- according to the individual antihypertensive response which can show high variability 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 or other components of the product, and in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or AV blocks of 2nd or 3rd degree.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4) the use of the product is contraindicated.

## **4.4 Special warnings and precautions for use**

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, depression, polyneuropathy and constipation.

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

Clonidine, the active ingredient of CATAPRES, and its metabolites are extensively excreted with the urine. Renal insufficiency requires particularly careful adjustment of dosage (see section 4.2).

As with other antihypertensive drugs, treatment with CATAPRES should be monitored particularly carefully in patients with heart failure or severe coronary disease.

In patients who have developed localised skin reaction to CATAPRES TTS transdermal patch, substitution of oral clonidine therapy may be associated with the development of a generalised rash.

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of CATAPRES after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headaches or nausea have been reported. When discontinuing therapy with CATAPRES, the physician should reduce the dose gradually over 2 - 4 days.

An excessive rise in blood pressure following discontinuation of CATAPRES therapy can be reversed by intravenous phentolamine or tolazoline (see section 4.5)

If long-term treatment with a beta-blocker has to be interrupted, then the beta-blocker should first be phased out gradually, followed by the clonidine.

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

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

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

CATAPRES tablets contain 205.5 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.

#### **4.5 Interactions with other medicines and other forms of interaction**

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 not alpha1-blocking agents.

Substances which raise blood pressure or induce a Na<sup>+</sup> 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 phentolamine or tolazoline may abolish the alpha2-receptor mediated effects of clonidine in a dose dependant 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. Studies with combined administration of clonidine and beta-receptor blockers have shown that if treatment is to be discontinued, the dose of the beta-receptor blocker 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 anti-depressants or neuroleptics with alpha-receptor blocking properties.

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

#### **4.6 Fertility, pregnancy and lactation**

##### ***Pregnancy (Category B3)***

There are limited amount of data from the use of clonidine in pregnant women.

During pregnancy, CATAPRES, as with any medication, should only be administered if the benefit justifies any possible risks to the foetus. Careful monitoring of mother and child is recommended. Clonidine passes the placental barrier and may lower the heart rate of the foetus. There is no adequate experience regarding the long-term effects or 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 (see section 5.3). Post partum a transient rise in blood pressure in the newborn cannot be excluded.

## ***Breast-feeding***

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

## ***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 (see section 5.3).

### **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 Undesirable effects**

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

#### Endocrine disorders:

gynaecomastia

#### Psychiatric disorders:

confusional state, delusional perception, depression, hallucination, libido decreased, nightmare, sleep disorder

#### Nervous system disorders:

dizziness, headache, paraesthesia, sedation

#### Eye disorder:

accommodation disorder, lacrimation decreased

#### Cardiac disorders:

atrioventricular block, bradyarrhythmia, sinus bradycardia

#### Vascular disorders:

orthostatic hypotension, Raynaud's phenomenon

#### Respiratory, thoracic and mediastinal disorders:

nasal dryness

#### Gastrointestinal disorders:

colonic pseudo-obstruction, constipation, dry mouth, nausea, salivary gland pain, vomiting

#### Skin and subcutaneous tissue disorders:

alopecia, pruritus, rash, urticaria

#### Reproductive system and breast disorders:

erectile dysfunction

#### General disorders and administration site conditions:

fatigue, malaise

#### Investigations:

blood glucose increased

### ***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

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

### **Symptoms**

Clonidine has a wide therapeutic range. Manifestations of intoxication are due to generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia somnolence including, coma, respiratory depression including apnoea. Paradoxical hypertension caused by stimulation of peripheral alpha1-receptors may occur.

### **Treatment**

Careful monitoring and symptomatic measures.

## 5. PHARMACOLOGICAL PROPERTIES

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### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Imidazoline receptor agonists, ATC code C02AC.

#### **Mechanism of action**

Clonidine acts primarily on the central nervous system, resulting in reduced sympathetic outflow and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact and therefore orthostatic symptoms are mild and infrequent. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse rate has been observed in most patients given clonidine, but the drug does not alter normal haemodynamic response to exercise.

### 5.2 Pharmacokinetic properties

#### **Absorption**

The pharmacokinetics of clonidine is dose-proportional in the range of 75 - 300 mcg. Clonidine, the active ingredient of CATAPRES, is well absorbed and undergoes a minor first pass effect. Peak plasma concentrations are reached within 1 - 3 h after oral administration. The pharmacokinetics of clonidine are not influenced by food nor by the race of the patient.

#### **Distribution**

The plasma protein binding is 30-40 %. Clonidine is rapidly and extensively distributed into tissues and crosses the blood brain barrier, as well as the placenta barrier. Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns.

#### **Biotransformation and elimination**

The terminal elimination half-life of clonidine has been found to range from 5 to 25.5 hours. It can be prolonged in patients with severely impaired renal function up to 41 hours. About 70% of the dose administered is excreted with the urine mainly in the form of the unchanged parent drug. The main metabolite p-hydroxy-clonidine is pharmacologically inactive. Approximately 20% of the total amount is excreted with 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.

### 5.3 Preclinical safety data

Single dose toxicity studies with clonidine were performed in different animal species by oral and parenteral routes of administration. The approximate oral LD50 values were 70 mg/kg (mouse), 190 mg/kg (rat), > 15 mg/kg (dog), and 150 mg/kg in monkeys. Following subcutaneous injection, the LD50 values were > 3 mg/kg in dogs and 153 mg/kg in rats. After intravenous administration the lethal dose ranges were between 6 mg/kg (dog) and < 21 mg/kg (rat).

Toxic trans-species signs of toxicity following exposure to clonidine were exophthalmus, ataxia and tremor, independently from the route of administration. At lethal doses, tonic-clonic convulsions occurred. In addition, excitement and aggressiveness alternating with sedation (mouse, rat, dog), salivation and tachypnea (dog) as well as hypothermia and apathy (monkey) were observed.

In repeated oral dose toxicity studies up to 18 months clonidine was well tolerated at 0.1 mg/kg (rat), 0.03 mg/kg (dog) and 1.5 mg/kg (monkey). In a 13 week study in rats, the no adverse effect level (NOAEL) was 0.05 mg/kg following subcutaneous administration. After intravenous administration rabbits and dogs tolerated 0.01 mg/kg/day for 5 and 4 weeks, respectively. Higher dosages caused hyperactivity, aggression, reduced food consumption and body weight gain (rat), sedation (rabbit) or an increase in heart and liver weight accompanied by elevated serum GPT, alkaline phosphatase and alpha-globulin levels and focal liver necroses (dog).

There were no signs of any teratogenic potential after oral administration in mouse and rat at 2.0 mg/kg and rabbit at 0.09 mg/kg, or after s.c. (0.015 mg/kg, rat) and i.v. treatment (0.15 mg/kg, rabbit). In rats, increases in resorption rate were observed at oral dosage of > 0.015 mg/kg/day; however dependent on duration of dosing. Fertility in rats was not impaired up to 0.15 mg/kg. Doses up to 0.075 mg/kg did not affect the peri- and postnatal development of the progeny.

There was no mutagenic potential in the Ames test and micronucleus assay in mice. Clonidine was not tumorigenic in a carcinogenicity assay in rats.

No local irritating or sensitising potential was found in guinea pigs and rabbits following i.v. and i.a. administrations.

## **6. PHARMACEUTICAL PARTICULARS**

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### **6.1 List of excipients**

#### Tablets

lactose monohydrate, calcium hydrogen phosphate anhydrous, maize starch dried, silica colloidal anhydrous, polyvidone, starch soluble, stearic acid.

#### Ampoules

sodium chloride, hydrochloric acid

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

#### Tablets

36 months

#### Ampoules

Unopened: 36 months

Once opened, use immediately and discard any unused contents.

### **6.4 Special precautions for storage**

#### Tablets

Store below 25°C

#### Ampoules

Store below 30°C

For storage conditions after first opening of the medicine, see section 6.3.

## **6.5 Nature and contents of container**

### Tablets

Blister pack PVC/PVdC/Al

Pack size of 100 tablets

### Ampoules

Colourless glass

Pack size 5 x 1 mL ampoules

## **6.6 Special precautions for disposal and other handling**

Any unused medicine or waste material should be disposed of in accordance with local requirements

## **7. MEDICINE SCHEDULE**

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Prescription medicine.

## **8. SPONSOR**

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Clinect NZ Pty Limited

C/- Ebos Group Limited

108 Wrights Road

Christchurch 8024

New Zealand

## **9. Free Call New Zealand: 0800 138 803 DATE OF FIRST APPROVAL**

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### Tablets

16 March 1972

### Ampoules

18 January 1973

## **10. DATE OF REVISION OF THE TEXT**

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30 October 2020

### ***Summary Table of Changes***

Section Changed	Summary of New Information
3	Update to define the symbol on the tablet
8	Sponsor Change