SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Catapres Tablets 100 micrograms
Clonidine Hydrochloride 100 micrograms Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100 micrograms of clonidine hydrochloride.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, circular, flat, bevel-edged tablets impressed with the identifying code 01C on one side.
01C

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets are indicated for the treatment of all grades of essential and secondary hypertension.

4.2 Posology and method of administration

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets are for oral administration only.

Adults:
Oral treatment should commence with 50 - 100 micrograms three times daily. This dose should be increased gradually every second or third day until control is achieved. Most patients will be controlled on divided daily doses of 300 - 1200 micrograms. However, some patients may require higher doses, e.g. 1800 micrograms or more.

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets may be added to an existing antihypertensive regimen where blood pressure control has not been satisfactorily achieved. If side-effects with existing therapy are troublesome the concomitant use of Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets may allow a lower dose of the

established regimen to be employed. Patients changing treatment should have their existing therapy reduced gradually whilst Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets are added to their regimen.

Patients undergoing anaesthesia should continue their Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets treatment before, during and after anaesthesia using oral or i.v. administration according to individual circumstances.

No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Paediatric Population:
There is insufficient evidence for the application of clonidine in children and adolescents younger than 18 years. Therefore the use of clonidine is not recommended in paediatric subjects under 18 years.

Patients with renal impairment:
Dosage must be adjusted

- according to the individual antihypertensive response which can show high variability in patients with renal insufficiency, careful monitoring is required (See Section 4.4)
- according to the degree of renal impairment

4.3 Contraindications

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets 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.

4.4 Special warnings and precautions for use

Caution should be exercised in patients with Raynaud's disease or other peripheral vascular disease. As with all drugs used in hypertension Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets should be used with caution in patients with cerebrovascular or coronary insufficiency.

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets 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 long-term treatment with Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets as there have been occasional reports of further depressive episodes during oral treatment in such patients.

As with other antihypertensive drugs, treatment with Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets should be monitored particularly carefully in patients with heart failure.

In hypertension caused by phaeochromocytoma no therapeutic effect of Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets can be expected.

Clonidine, the active ingredient of this medicinal product, 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 (See Section 4.2); 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 Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets, 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 Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets are being given concurrently with a beta-blocker, Catapres Tablets /Clonidine Hydrochloride 100 micrograms Tablets should not be discontinued until several days after the withdrawal of the beta-blocker.

Patients who wear contact lenses should be warned that treatment with Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets 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.

4.5 Interaction with other medicinal products 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 the effect of alpha$_1$-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 alpha$_2$-receptor blocking properties, such as mirtazapine, may abolish the alpha$_2$-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.

4.6 Fertility, pregnancy and lactation

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 Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets 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.

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 Tablets/Clonidine Hydrochloride 100 micrograms Tablets. 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.

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

<u>Endocrine disorders:</u>	
Gynaecomastia	rare
<u>Psychiatric disorders:</u>	
Confusional state	not known
Delusional perception	uncommon
Depression	common
Hallucination	uncommon
Libido decreased	not known
Nightmare	uncommon
Sleep disorder	common
<u>Nervous system disorders:</u>	
Dizziness	very common
Headache	common
Paraesthesia	uncommon
Sedation	very common
<u>Eye disorders:</u>	
Accommodation disorder	not known
Lacrimation decreased	rare
<u>Cardiac disorders:</u>	
Atrioventricular block	rare
Bradyarrhythmia	not known
Sinus bradycardia	uncommon
<u>Vascular disorders:</u>	
Orthostatic hypotension	very common
Raynaud's phenomenon	uncommon
<u>Respiratory, thoracic and mediastinal disorders:</u>	
Nasal dryness	rare
<u>Gastrointestinal disorders:</u>	
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.

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 alpha$_1$-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.

5.1 Pharmacodynamic properties

Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets have been shown to have both central and peripheral sites of action. With long-term treatment Catapres Tablets/Clonidine Hydrochloride 100 micrograms Tablets reduce 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.

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 (see section 4.2).

5.2 Pharmacokinetic properties

Absorption and distribution

The pharmacokinetics of clonidine is dose-proportional in the range of 75-300 micrograms; over this range, dose linearity has not been fully demonstrated. Clonidine, the active ingredient of this medicinal product, is highly absorbed and undergoes a minor first pass effect. Peak plasma concentrations are reached within 1-3 h after oral administration. 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 placental barrier. Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns.

Metabolism 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 form of the unchanged parent drug (40-60% of the dose). The main metabolite p-hydroxy-clonidine is pharmacologically inactive. Approximately 20% of the total amount is excreted with the faeces. There is no definitive data about food or race effects on 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 renal function. The hypotensive effect is attenuated or decreases with plasma concentrations above 2.0 ng/ml.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Calcium hydrogen phosphate (anhydrous)
Maize starch, dried
Colloidal silica (anhydrous)
Povidone
Modified starch (corn starch, oxidized)
Stearic acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Keep the blisters in the outer carton

6.5 Nature and contents of container

Opaque PVC 250µm thick/PVDC 40 g/m^2 blisters with aluminium lidding foil 20µm in packs of 100 tablets.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

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PL 22824/0010

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