Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Catapres Tablets 300 micrograms

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains clonidine hydrochloride 300 micrograms.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, round, flat, bevel-edged tablets impressed with the motif **03C** / **03C** on one side and the Boehringer Ingelheim symbol on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Catapres tablets are indicated for the treatment of hypertension that has failed to respond adequately to other anti-hypertensives.

4.2 Posology and method of administration

Adults only:
The usual initial dosage is 0.05 to 0.10 mg three times daily with subsequent gradual increments to the level of optimal control generally in the daily dose range of 0.3 to 1.2mg in divided doses although higher levels may be required.

Should clonidine be added to other anti-hypertensive therapy dosage of the latter should be gradually reduced as the clonidine is introduced.

Patients undergoing anaesthesia should continue their Catapres treatment before, during and after anaesthesia using oral or intravenous administration according to individual circumstances.

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.

4.3 Contraindications

Catapres should not be used in children (please refer to section 4.4 Special Warnings and Precautions for Use) or 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

Clonidine should only be used with caution in patients with depression or a history thereof, with Raynaud's disease, or other peripheral vascular occlusive disease. The product should only be used with caution in patients with cerebrovascular or coronary insufficiency. Catapres should also be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, and with polyneuropathy or constipation.

As with other antihypertensive drugs, treatment with Catapres should be monitored particularly carefully in patients with heart failure.

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 in the urine. Dosage must be adjusted according to the individual antihypertensive response, which can show high variability in patients with renal insufficiency; 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 clonidine should be avoided because of possible 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 long-term treatment with a beta-receptor blocker has to be interrupted then the beta-receptor blocker should first be phased out gradually, followed by gradual withdrawal of clonidine.

Patients who wear contact lenses should be warned that treatment with Catapres may cause decreased lacrimination.

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.

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.

This product contains 72.1 mg of lactose per tablet. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 concomitant use of other central nervous system depressants will increase the depressant effect of the drug.

4.6 Fertility, pregnancy and lactation

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 new-born cannot be excluded.

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

There is no adequate experience regarding the long-term effects of prenatal exposure.

The use of Catapres during lactation is not recommended due to a lack of supporting information.

4.7 Effects on ability to drive and use machines

This product may cause drowsiness. Patients receiving it should not drive or operate machinery unless it has been shown not to affect physical or mental ability.

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, < 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

Nervous system disorders:	
Dizziness	very common
Headache	common
Paraesthesia	uncommon
Sedation	very common
Eye disorders:	
Accommodation disorder	not known
Lacrimation decreased	rare
Cardiac disorders:	
Atrioventricular block	rare
Bradyarrhythmia	not known
Sinus bradycardia	uncommon
Vascular disorders:	
Orthostatic hypotension	very common
Raynaud's phenomenon	uncommon
Respiratory, thoracic and mediastinal disorders:	
Nasal dryness	rare
Gastrointestinal disorders:	
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

Fluid retention occurs occasionally. Two cases of hepatitis have also been reported.

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 10mg.

Treatment:
Gastric lavage should be performed where appropriate. In most cases all that is required are general supportive measures. Where bradycardia is severe atropine will increase the heart rate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

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

The pharmacokinetics of clonidine is dose-proportional in the range of 100-600 micrograms. Clonidine, the active ingredient of Catapres, is well absorbed and no first pass effect exists. Peak plasma concentrations are reached within 1-3 h after oral administration. Clonidine is rapidly and extensively distributed into tissues and crosses the blood-brain barrier as well as the placental barrier. The plasma protein binding is 30-40%.

The mean plasma half-life of clonidine is about 13 hours ranging between 10 and 20 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 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. The pharmacokinetics of clonidine are not influenced by food nor by the race of the patient.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 1.5 ng/ml in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.

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
Colloidal silica (anhydrous)
Povidone
Soluble starch
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 250 μm/PVDC 40g/m^2 blisters with aluminium lidding foil 20 μm containing 100 tablets.

Not all pack sizes are marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
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Bracknell
Berkshire RG12 8YS
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 7/14/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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