Catapres®

Clonidine hydrochloride

Composition

1 ampoule of 1 ml contains 0.150 mg
2,6-dichloro-N-2-imidazolidinylidenebenzenamine hydrochloride
(= clonidine hydrochloride)

Excipients:
ampoules: Sodium chloride, hydrochlorid acid

Indications

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

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

Dosage and administration

Treatment of hypertension requires regular medical supervision.

The dose of CATAPRES® must be adjusted according to the patient's individual blood pressure response.

Ampoules

Subcutaneous or i.m. injection of an ampoule containing 0.150 mg CATAPRES® should only be carried out in 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 0.15 mg should be used per infusion.
If necessary, ampoules can be administered parenterally up to 4 times daily.
This medicinal product contains 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 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.

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 block of 2nd or 3rd degree.

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

Special warnings and precautions

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, polyneuropath, 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 Dosage and Administration).
As with other antihypertensive drugs, treatment with CATAPRES® should be monitored particularly carefully in patients with heart failure or severe coronary heart disease.

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, headache 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 Interactions).

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

In patients who have developed localized skin reaction to transdermal clonidine, administration of oral clonidine therapy may be associated with the development of a generalized rash.

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 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 ADHS, serious adverse reactions, including death, have been observed. Therefore, clonidine in this combination is not recommended.

Interactions

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 alpha$_1$-blocking agents.

Substances which raise blood pressure or induce a 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 phentolamine or tolazoline 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.

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

Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of clonidine in pregnant women.
During pregnancy CATAPRES®, as any drug, should only be administered if clearly needed. 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 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 (see section Toxicology).
Post partum a transient rise in blood pressure in the newborn cannot be excluded.

Lactation

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 Toxicology).

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.

Side 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

Overdose

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 alpha$_1$-receptors may occur.

Treatment

Careful monitoring and symptomatic measures.

Pharmacological 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 hemodynamic response to exercise.

Pharmacokinetics

Absorption and distribution

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 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. Approx. 20 % of the total amount is excreted with the faeces.

The pharmacokinetics of clonidine is not influenced by food nor by the race of the patient. 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.

Toxicology

Single dose toxicity studies with clonidine were performed in different animal species by oral and parenteral routes of administration. The approximate oral LD_{50} values were 70 mg/kg (mouse), 190 mg/kg (rat), > 15 mg/kg (dog), and 150 mg/kg in monkeys. Following subcutaneous injection, the LD_{50} 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 sensitizing potential was found in guinea pigs and rabbits following i.v. and i.a. administrations.

Availability

Ampoule of CATAPRES 150 mcg/ml Reg. No. DKI……..
Box ,10 ampoules @1 ml

Store in temperature below 30 °C, Protect from light.
Store in a safe place, out of reach of children.

Only on doctor's prescription.
Hanya dengan resep dokter.

Manufactured by:
Boehringer Ingelheim Espana, SA
San Cugat del Valles
Spain

Registered by:
PT Tunggal Idaman Abdi
Jl. Jend. Ahmad Yani No. 7
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