

New Zealand Datasheet

1 PRODUCT NAME

CATAPRES® - TTS®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clonidine

3 PHARMACEUTICAL FORM

Transdermal Therapeutic System No. 1 (Patch): 2.5mg/3.5cm², printed with Company symbol and BI 31.

Transdermal Therapeutic System No. 2 (Patch): 5mg/7.0cm², printed with Company symbol and BI 32.

Transdermal Therapeutic System No. 3 (Patch): 7.5mg/10.5cm², printed with Company symbol and BI 33.

The rate of release of clonidine and content of clonidine in each system is given in the table below:

| | Programmed Delivery <i>In vivo</i> /day Over 1 week | Clonidine content (mg) | Size (cm ²) |
|----------------|--|------------------------------|----------------------------|
| CATAPRES-TTS-1 | 0.1mg | 2.5 | 3.5 |
| CATAPRES-TTS-2 | 0.2mg | 5.0 | 7.0 |
| CATAPRES-TTS-3 | 0.3mg | 7.5 | 10.5 |

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CATAPRES-TTS is indicated for the treatment of mild to moderate hypertension. It can be used as monotherapy or concomitantly with other antihypertensive agents if required to enhance hypotensive effect.

4.2 Dose and method of administration

CATAPRES-TTS dosage should be titrated according to individual patient's therapeutic requirements. Commence with one CATAPRES-TTS-1 applied weekly to a freshly cleaned, hairless area of the upper outer arm or chest. A new site should be used each week when applying new patches. If the system loosens during 7-day wearing, the adhesive cover should be applied directly over the system to ensure good adhesion. There have been rare reports of the need for patch changes prior to 7 days to maintain blood pressure control.

If after one to two weeks the desired reduction in blood pressure is not achieved, increase the weekly dosage by changing to CATAPRES-TTS-2. If this dosage is still not satisfactory after 1-2 weeks therapy then increase the weekly dosage by changing to CATAPRES-TTS-3.

Most patients with mild to moderate hypertension will be controlled on one CATAPRES-TTS-3 or less. In more resistant cases where blood pressure is not satisfactorily controlled on one CATAPRES-TTS-3, it is recommended that a diuretic and/or other antihypertensive agents be added to enhance the hypotensive effect. In this way, the dose of each individual drug may be reduced and side effects minimised. Higher doses of up to two CATAPRES-TTS-3 a week have been utilised. An increase in dosage above two CATAPRES-TTS-3 is usually not associated with additional efficacy.

When substituting CATAPRES-TTS in patients on prior oral antihypertensive therapy, including oral CATAPRES, physicians should be aware that the antihypertensive effect of CATAPRES-TTS might not commence until 2-3 days after initial application. Therefore, gradual reduction of prior drug dosage over 5-6 days is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

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 the renal impairment.

Careful monitoring is required. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

4.3 Contraindications

CATAPRES-TTS 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.

4.4 Special warnings and precautions for use

CATAPRES-TTS 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.

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

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

Physicians considering starting CATAPRES-TTS therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 - 3 days after initial application of CATAPRES-TTS.

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

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of CATAPRES-TTS 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-TTS, the physician should reduce the dose gradually over 2-4 days.

An excessive rise in blood pressure following discontinuation of CATAPRES-TTS therapy can be reversed by administration of oral clonidine hydrochloride or by intravenous phentolamine (see 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 localised contact sensitisation to CATAPRES-TTS, substitution of oral clonidine therapy may in rare instances be associated with development of a generalised skin rash.

Patients should be instructed to consult their physicians promptly about the possible need to remove the patch if they observe moderate to severe localized erythema and/or vesicle formation at the site of application or generalized skin rash.

If a patient experiences isolated, mild localized skin irritation before completing 7 days of use, the system may be removed and replaced with a new system applied to a fresh skin site.

CATAPRES-TTS therapy should not be interrupted during the surgical period. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required. Physicians considering starting CATAPRES-TTS therapy during the perioperative period must be aware that therapeutic plasma clonidine levels are not achieved until 2 to 3 days after initial application of CATAPRES-TTS (see Dosage and Administration).

CATAPRES-TTS should be removed before attempting defibrillation or cardioversion because of the potential for altered electrical conductivity which may increase the risk of arcing, a phenomenon associated with the use of defibrillators.

Because the CATAPRES-TTS contains aluminum, it is recommended to remove the system before undergoing an MRI. Skin burns have been reported at the patch site in several patients wearing an aluminized transdermal patch during a magnetic resonance imaging scan (MRI).

Patients who wear contact lenses should be warned that treatment with CATAPRES-TTS 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 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.

4.5 Interaction 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 α_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 α_2 -receptor blocking properties such as phentolamine or tolazoline may abolish the α_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 α -receptor blocking properties.

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

4.6 Fertility, pregnancy and lactation

Use in pregnancy

No adequate well-controlled studies have been conducted in pregnant women.

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

Preclinical studies with clonidine in rats and rabbits have not shown teratogenic effects. In rats, increased resorption rates were observed after oral dosing of clonidine (please refer to section Toxicology).

Post partum a transient rise in blood pressure in the newborn cannot be excluded.

During pregnancy CATAPRES-TTS, as any drug, should only be administered if clearly needed. Careful monitoring of mother and child is recommended.

Use in lactation

Clonidine passes the placenta barrier and may lower the heart rate of the foetus.

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

The use of CATAPRES-TTS during lactation is not recommended due to a lack of supporting information.

Effects on fertility

No clinical studies on the effect on human fertility have been conducted with clonidine. Animal studies with clonidine did not indicate 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-TTS. 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.

Psychiatric disorders:

depression
sleep disorder
confusional state
delusional perception
hallucination
libido decreased
nightmare

Nervous system disorders:

dizziness
sedation
headache
paraesthesia

Eye disorders:

accommodation disorder
lacrimation decreased

Cardiac disorders:

bradyarrhythmia
sinus bradycardia
atrioventricular block

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:

application site erythema
application site erosion
application site burn
application site discolouration
application site papules
application site dermatitis
urticaria
pruritus
rash
alopecia

Reproductive system and breast disorders:

erectile dysfunction
gynecomastia

General disorders and administration site conditions:

application site pain
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

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 apnea. Paradoxical hypertension caused by stimulation of peripheral α_1 -receptors may occur.

Rare cases of CATAPRES-TTS poisoning due to accidental or deliberate mouthing or ingestion of the patch have been reported, most of them involving children.

Treatment

Careful monitoring and symptomatic measures. There is no specific antidote for clonidine overdose. If symptoms of poisoning occur following dermal exposure, remove all CATAPRES-TTS. After their removal, the plasma clonidine levels will persist for about 8 hours, then decline slowly over a period of several days.

In case of accidental overdose, symptomatic treatments and supportive care are suggested. For information on the management of overdose, contact the National Poisons Centre on 0800 764 766.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiadrenergic agents, centrally acting, imidazoline receptor agonists ATC Code C02AC01

Clonidine stimulates alpha-adrenoreceptors in the brain stem. This action results in reduced sympathetic outflow from the central nervous system and in decreases 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.

Tolerance to the antihypertensive effect may develop in some patients, necessitating a re-evaluation of therapy.

5.2 Pharmacokinetic properties

Clonidine is released from the CATAPRES-TTS transdermal patch at a relatively constant rate of $4.32 \pm 1.68 \mu\text{g/h}$ for 7 days. Steady-state clonidine plasma levels are obtained within three days after transdermal application to the upper outer arm and increase linearly with increasing size of the transdermal patch. Mean steady-state plasma concentrations with the 3.5 cm², 7.0 cm² and 10.5 cm² systems are approx. 0.4 ng/ml, 0.8 ng/ml and 1.1 ng/ml, respectively. Comparable clonidine steady-state concentrations are reached after application to the chest. Effective clonidine plasma concentrations are reached within 2 - 3 days after application of the first system. Steady-state clonidine plasma levels remain constant after removal of one system and application of a new system of the same size.

Kinetic parameters of clonidine were calculated from plasma concentrations after i.v. administration. The absolute bioavailability of clonidine from the CATAPRES-TTS dosage form is approximately 60%. The apparent volume of distribution (V_z) of clonidine is 197 L (2.9 L/kg). The drug crosses the blood-brain-barrier as well as the placenta-barrier. The plasma protein binding is 30-40%. Clonidine has a total clearance of 177 ml/min and a renal clearance of 102 ml/min. Plasma elimination half-life of clonidine determined after i.v. application is approximately 13 hours. After removal of the CATAPRES-TTS clonidine plasma concentrations decline slowly with

a half-life of approximately 20 hours, reflecting the slower absorption from the CATAPRES-TTS. Plasma elimination half-life can be prolonged in patients with severely impaired renal function up to 41 hours.

In an excretion balance study cumulative renal excretion (3-5 days) of drug-related radioactivity (including parent compound and all metabolites) accounted for 65% and total radioactivity excreted via the faeces was 22% after oral administration. Approximately 40-60% of the total radioactivity recovered in the urine within 24 hours accounts for the unchanged parent compound. The remainder of the urinary radioactivity consists of 5 clonidine metabolites, which are mainly formed in the liver and pharmacologically inactive.

5.3 Preclinical safety data

Single-dose toxicity studies with clonidine revealed approximative oral LD₅₀ values between >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 LD₅₀ values were between 6 mg/kg (dog) and <21 mg/kg (rat). Clinical signs post dose were exophthalmus, ataxia and tremor, independently from the route of administration. 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 oral repeat-dose toxicity studies clonidine was tolerated at 0.1 mg/kg/day and 0.03 mg/kg/day (rat, 18 months and dog, 52 weeks, respectively). In a 52-week oral study in the monkey, the no observed adverse effect level (NOAEL) was 1.5 mg/kg/day. In a 13 week subcutaneous study in rats, the NOAEL was 0.05 mg/kg/day. In intravenous studies, rabbits and dogs tolerated 0.01 mg/kg/day and 0.1 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 the mouse and the rat at 2.0 mg/kg/day - as well as in the rabbit at 0.09 mg/kg/day, or after s.c. (0.016 mg/kg/day, rat) and i.v. treatment (0.15 mg/kg/day, rabbit). In rats, increases in resorption rate were observed at oral dosage of ≥ 0.015 mg/kg/day (equivalent to about 1/8 the oral MRHDD based on a mg/m² basis); however dependent on duration of dosing. In rats, up to oral dosages of 0.15 mg/kg/day (about the oral MRHDD based on a mg/m² basis) fertility index and peri- and postnatal development of the progeny were not impaired.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Light liquid paraffin, polyisobutylene, colloidal anhydrous silica, medium-density polyethylene (MDPA)/aluminium-polyester (AL/PET)/ethylene vinyl acetate copolymer (EVA) pigmented film, microporous polypropylene film, fluorocarbon diacrylate-coated (FCD)/polyester (PET) film.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months from date of manufacture

6.4 Special precautions for storage

Store below 30°C.

Store in a safe place out of the reach of children.

6.5 Nature and contents of container

Patch, TTS-1, 2 and 3, 4s.

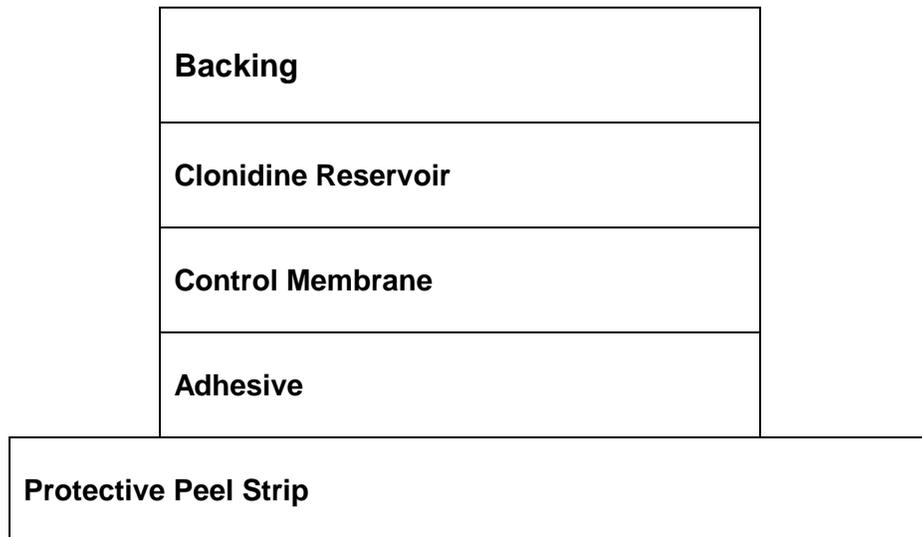
System Structure and Components

CATAPRES-TTS is a multi-layered film, 0.2mm thick, containing clonidine as the active agent. System area is 3.5, 7.0 or 10.5cm² and the amount of drug released is directly proportionally to area. The composition per unit area of all three dosages is identical.

Proceeding from the visible surface towards the surface attached to the skin are four layers:

1. a backing layer of pigmented polyester film;
2. a drug reservoir of clonidine, mineral oil, polyisobutylene and colloidal silicon dioxide;
3. a microporous polypropylene membrane that controls the rate of delivery of clonidine from the system to the skin surface;
4. an adhesive formulation of clonidine, mineral oil, polyisobutylene, and colloidal silicon dioxide. Prior to use, a protective peel strip of polyester that covers layer 4 is removed.

Cross Section of the System



6.6 Special precautions for disposal

No special precautions required.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

CARSL Consulting

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9 DATE OF FIRST APPROVAL

12 December 1984

10 DATE OF REVISION OF THE TEXT

1 February 2019