CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 18891/S015

FINAL PRINTED LABELING

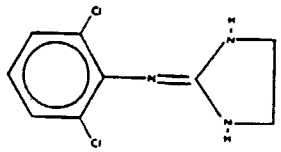
Catapres-TTS®
(clonidine)

Catapres TTS® -1
Catapres TTS® -2
Catapres TTS® -3

Transdermal Therapeutic System
Programmed delivery *in vivo* of 0.1, 0.2, or 0.3 mg clonidine per day, for one week.

Prescribing Information

DESCRIPTION Catapres-TTS® (clonidine) is a transdermal system providing continuous systemic delivery of clonidine for 7 days at an approximately constant rate. Clonidine is a centrally acting alpha-agonist hypotensive agent. It is an imidazoline derivative with the chemical name 2, 6-dichloro-N-2-imidazolidinylidene-benzenamine and has the following chemical structure:

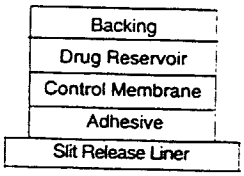


(clonidine)

System Structure and Components Catapres-TTS is a multilayered film, 0.2 mm thick, containing clonidine as the active agent. The system areas are 3.5 cm² (CATAPRES-TTS-1), 7.0 cm² (CATAPRES-TTS-2) and 10.5 cm² (CATAPRES-TTS-3) and the amount of drug released is directly proportional to the area (See Release Rate Concept). The composition per unit area is the same for all three doses.

Proceeding from the visible surface towards the surface attached to the skin, there are four consecutive 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 slit release liner of polyester that covers the adhesive layer is removed.

Cross Section of the System.



Release Rate Concept Catapres-TTS is programmed to release clonidine at an approximately constant rate for 7 days. The energy for drug release is derived from the concentration gradient existing between a saturated solution of drug in the system and the much lower concentration prevailing in the skin. Clonidine flows in the direction of the lower concentration at a constant rate, limited by the rate-controlling membrane, so long as a saturated solution is maintained in the drug reservoir.

Following system application to intact skin, clonidine in the adhesive layer saturates the skin site below the system. Clonidine from the drug reservoir then begins to flow through the rate-controlling membrane and the adhesive layer of the system into the systemic circulation via the capillaries beneath the skin. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application of Catapres-TTS.

The 3.5, 7.0, and 10.5 cm² systems deliver 0.1, 0.2, and 0.3 mg of clonidine per day, respectively. To ensure constant release of drug for 7 days, the total drug content of the system is higher than the total amount of drug delivered. Application of a new system to a fresh skin site at weekly intervals continuously maintains therapeutic plasma concentrations of clonidine. If the Catapres-TTS is removed and not replaced with a new system, therapeutic plasma clonidine levels will persist for about 8 hours and then decline slowly over several days. Over this time period, blood pressure returns gradually to pretreatment levels.

CLINICAL PHARMACOLOGY 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; therefore, orthostatic symptoms are mild and infrequent.

Acute studies with clonidine hydrochloride in humans have demonstrated a moderate reduction (15% to 20%) of cardiac output in the supine position with no change in the peripheral resistance; at a 45° tilt there is a smaller reduction in cardiac output and a decrease of peripheral resistance.

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 responses to exercise.

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

Other studies in patients have provided evidence of a reduction in plasma renin activity and in the excretion of aldosterone and catecholamines. The exact relationship of these pharmacologic actions to the antihypertensive effect of clonidine has not been fully elucidated.

Clonidine acutely stimulates the release of growth hormone in children as well as adults but does not produce a chronic elevation of growth hormone with long-term use.

Pharmacokinetics The plasma half-life of clonidine is 12.7 ± 7 hours. Following oral administration, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug within 24 hours. The remainder of the absorbed dose is metabolized in the liver.

INDICATIONS AND USAGE Catapres-TTS® (clonidine) is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS Catapres-TTS® (clonidine) should not be used in patients with known hypersensitivity to clonidine or to any other component of the therapeutic system.

WARNINGS Withdrawal Patients should be instructed not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and confusion accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. The likelihood of such reactions to discontinuation of clonidine therapy appears to be greater after administration of higher doses or continuation of concomitant beta-blocker treatment and special caution is therefore advised in these situations. Rare instances of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy with Catapres®, the physician should reduce the dose gradually over 2 to 4 days to avoid withdrawal symptomatology.

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. If therapy is to be discontinued in patients receiving a beta-blocker and clonidine concurrently, the beta-blocker should be withdrawn several days before the gradual discontinuation of Catapres-TTS®.

PRECAUTIONS General In patients who develop localized contact sensitization to Catapres-TTS (clonidine) continuation of Catapres-TTS or substitution of oral clonidine hydrochloride therapy may be associated with development of a generalized skin rash.

In patients who develop an allergic reaction to Catapres-TTS, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

Catapres-TTS should be used with caution in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure.

In rare instances, loss of blood pressure control has been reported in patients using Catapres-TTS according to the instructions for use.

Perioperative Use 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).

Defibrillation or Cardioversion The transdermal clonidine systems 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.

Information for Patients Patients should be cautioned against interruption of Catapres-TTS therapy without their physician's advice.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. They should also be informed that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

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.

If the system should begin to loosen from the skin after application, the patient should be instructed to place the adhesive overlay directly over the system to ensure adhesion during its 7-day use.

Used Catapres-TTS patches contain a substantial amount of their initial drug content which may be harmful to infants and children if accidentally applied or ingested. THEREFORE, PATIENTS SHOULD BE CAUTIONED TO KEEP BOTH USED AND UNUSED CATAPRES-TTS PATCHES OUT OF THE REACH OF CHILDREN. After use, Catapres-TTS should be folded in half with the adhesive sides together and discarded away from children's reach.

Instructions for use, storage and disposal of the system are provided at the end of this monograph. These instructions are also included in each box of Catapres-TTS.

Drug Interactions Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving clonidine is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.

Due to a potential for additive effects such as bradycardia and AV block, caution is warranted in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction e.g., digitalis, calcium channel blockers and beta-blockers.

Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats. (See TOXICOLOGY.)

Toxicology In several studies with oral clonidine hydrochloride, a dose-dependent increase in the incidence and severity of spontaneous retinal degeneration was seen in albino rats treated for six months or longer. Tissue distribution studies in dogs and monkeys showed a concentration of clonidine in the choroid.

In view of the retinal degeneration seen in rats, eye examinations were performed during clinical trials in 908 patients before, and periodically after, the start of clonidine therapy. In 353 of these 908 patients, the eye examinations were carried out over periods of 24 months or longer. Except for some dryness of the eyes, no drug-related abnormal ophthalmological findings were recorded and, according to specialized tests such as electroretinography and macular dazzle, retinal function was unchanged.

In combination with amitriptyline, clonidine hydrochloride administration led to the development of corneal lesions in rats within 5 days.

Carcinogenesis, Mutagenesis, Impairment of Fertility Chronic dietary administration of clonidine was not carcinogenic to rats (132 weeks) or mice (78 weeks) dosed, respectively, at up to 46 to 70 times the maximum recommended daily human dose as mg/kg (9 or 6 times the MRDHD) on a mg/m² basis). There was no evidence of genotoxicity in the Ames test for mutagenicity or mouse micronucleus test for clastogenicity.

Fertility of male and female rats was unaffected by clonidine doses as high as 150 mcg/kg (approximately 3 times the MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000 mcg/kg (10 to 40 times the oral MRDHD on a mg/kg basis; 2 to 8 times the MRDHD on a mg/m² basis).

Pregnancy *TERATOGENIC EFFECTS Pregnancy Category C* Reproduction studies performed in rabbits at doses up to approximately 3 times the oral maximum recommended daily human dose (MRDHD) of Catapres® (clonidine hydrochloride) produced no evidence of a teratogenic or embryotoxic potential in rabbits. In rats, however, doses as low as 1/3 the oral MRDHD (1/15 the MRDHD on a mg/m² basis) of clonidine were associated with increased resorptions in a study in which dams were treated continuously from 2 months prior to mating. Increased resorptions were not associated with treatment at the same or at higher dose levels (up to 3 times the oral MRDHD) when the dams were treated on gestation days 6 - 15. Increases in resorption were observed at much higher dose levels (40 times the oral MRDHD on a mg/kg basis; 4 to 8 times the MRDHD on a mg/m² basis) in mice and rats treated on gestation days 1 - 14 (lowest dose employed in the study was 500 mcg/kg).

No adequate well-controlled studies have been conducted in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers As clonidine is excreted in human milk, caution should be exercised when Catapres-TTS is administered to a nursing woman.

Pediatric Use Safety and effectiveness in pediatric patients below the age of twelve have not been established (See Warnings on Withdrawal).

ADVERSE REACTIONS Clinical trial experience with Catapres-TTS Most systemic adverse effects during Catapres-TTS therapy have been mild and have tended to diminish with continued therapy. In a 3-month multiclinic trial of Catapres-TTS in 101 hypertensive patients, the systemic adverse reactions were, dry mouth (25 patients) and drowsiness (12) fatigue (6), headache (5), lethargy and sedation (3 each), insomnia, dizziness, impotence/sexual dysfunction, dry throat (2 each) and constipation, nausea, change in taste and nervousness (1 each).

In the above mentioned 3-month controlled clinical trial, as well as other uncontrolled clinical trials, the most frequent adverse reactions were dermatological and are described below.

In the 3-month trial, 51 of the 101 patients had localized skin reactions such as erythema (26 patients) and/or pruritus, particularly after using an adhesive overlay throughout the 7-day dosage interval. Allergic contact sensitization to Catapres-TTS was observed in 5 patients. Other skin reactions were localized vesiculation (7 patients), hyperpigmentation (5), edema (3), excoriation (3), burning (3), papules (1), throbbing (1), blanching (1), and a generalized macular rash (1).

In additional clinical experience, contact dermatitis resulting in treatment discontinuation was observed in 128 of 673 patients (about 19 in 100) after a mean duration of treatment of 37 weeks. The incidence of contact dermatitis was about 34 in 100 among white women, about 18 in 100 in white men, about 14 in 100 in black women, and approximately 8 in 100 in black men. Analysis of skin reaction data showed that the risk of having to discontinue Catapres-TTS treatment because of contact dermatitis was greatest between treatment weeks 6 and 26, although sensitivity may develop either earlier or later in treatment.

In a large-scale clinical acceptability and safety study by 451 physicians in a total of 3539 patients, other allergic reactions were recorded for which a causal relationship to Catapres-TTS was not established: maculopapular rash (10 cases); urticaria (2 cases); and angioedema of the face (2 cases), which also affected the tongue in one of the patients.

Marketing Experience with Catapres-TTS Other adverse effects reported since the drug has been marketed are listed below by body system. In this setting, an incidence or causal relationship cannot always be accurately determined. However, none of the events listed below occurred in a frequency greater than 0.5%.

Body as a Whole Fever; malaise; weakness; and pallor; and withdrawal syndrome.

Cardiovascular Congestive heart failure; cerebrovascular accident; electrocardiographic abnormalities (i.e., bradycardia, sick sinus syndrome disturbances and arrhythmias); chest pain; orthostatic symptoms; syncope, increases in blood pressure; sinus bradycardia and atrioventricular block with and without the use of concomitant digitalis; Raynaud's phenomenon; tachycardia; bradycardia; and palpitations.

Central and Peripheral Nervous System/Psychiatric Delirium; mental depression; visual and auditory hallucinations; localized numbness; vivid dreams or nightmares; restlessness; anxiety; agitation; irritability; other behavioral changes; and drowsiness.

Dermatological Angioneurotic edema; localized or generalized rash; hives; urticaria; contact dermatitis; pruritus; alopecia; and localized hypo or hyper pigmentation.

Gastrointestinal Anorexia and vomiting.

Genitourinary Difficult micturition; loss of libido; and decreased sexual activity.

Metabolic Gynecomastia or breast enlargement and weight gain.

Musculoskeletal Muscle or joint pain; and leg cramps.

Ophthalmological Blurred vision; burning of the eyes and dryness of the eyes.

Adverse Events Associated with Oral Catapres Therapy: Most adverse effects are mild and tend to diminish with continued therapy. The most frequent (which appear to be dose-related) are dry mouth, occurring in about 40 of 100 patients; drowsiness, about 33 in 100; dizziness, about 16 in 100; constipation and sedation, each about 10 in 100. The following less frequent adverse experiences have also been reported in patients receiving Catapres (clonidine hydrochloride USP), but in many cases patients were receiving concomitant medication and a causal relationship has not been established.

Body as a Whole Weakness, about 10 in 100 patients; fatigue, about 4 in 100; headache and withdrawal syndrome each about 1 in 100. Also reported were pallor; a weakly positive Coombs' test; increased sensitivity to alcohol; and fever.

Cardiovascular Orthostatic symptoms, about 3 in 100 patients; palpitations and tachycardia, and bradycardia, each about 5 in 1000. Syncope, Raynaud's phenomenon, congestive heart failure, and electrocardiographic abnormalities (i.e. sinus node arrest, functional bradycardia, high degree AV block and arrhythmias) have been reported rarely. Rare cases of sinus bradycardia and AV block have been reported, both with and without the use of concomitant digitalis.

Central Nervous System Nervousness and agitation, about 3 in 100 patients, mental depression, about 1 in 100 and insomnia, about 5 in 1000. Other behavioral changes, vivid dreams or nightmares, restlessness, anxiety, visual and auditory hallucinations and delirium have rarely been reported.

Dermatological Rash, about 1 in 100 patients; pruritus, about 7 in 1000; hives, angioneurotic edema and urticaria, about 5 in 1000; alopecia, about 2 in 1000.

Gastrointestinal Nausea and vomiting, about 5 in 100 patients; anorexia and malaise, each about 1 in 100; mild transient abnormalities in liver function tests, about 1 in 100; hepatitis, parotitis, constipation, pseudo-obstruction, and abdominal pain, rarely.

Genitourinary Decreased sexual activity, impotence and loss of libido, about 3 in 100 patients; nocturia, about 1 in 100; difficulty in micturition, about 2 in 1000; urinary retention, about 1 in 1000.

Hematologic Thrombocytopenia, rarely.

Metabolic Weight gain, about 1 in 100 patients; gynecomastia, about 1 in 1000; transient elevation of blood glucose or serum creatine phophokinase, rarely.

Musculoskeletal Muscle or joint pain, about 6 in 1000 and leg cramps, about 3 in 1000.

Oro-otolaryngeal Dryness of the nasal mucosa was rarely reported.

Ophthalmological Dryness of the eyes, burning of the eyes and blurred vision were reported.

OVERDOSAGE Hypertension may develop early and may be followed by hypotension, bradycardia, respiratory depression, hypothermia, drowsiness, decreased or absent reflexes, weakness, irritability and miosis. The frequency of CNS depression may be higher in children than adults. Large overdoses may result in reversible cardiac conduction defects or dysrhythmias, apnea, coma and seizures. Signs and symptoms of overdose generally occur within 30 minutes to two hours after exposure. As little as 0.1 mg of clonidine has produced signs of toxicity in children.

If symptoms of poisoning occur following dermal exposure, remove all Catapres-TTS systems. After their removal, the plasma clonidine levels will persist for about 8 hours, then decline slowly over a period of several days. Rare cases of Catapres-TTS poisoning due to accidental or deliberate mouthing or ingestion of the patch have been reported, many of them involving children.

There is no specific antidote for clonidine overdosage. Ipecac syrup-induced vomiting and gastric lavage would not be expected to remove significant amounts of clonidine following dermal exposure. If the patch is ingested, whole bowel irrigation may be considered and the administration of activated charcoal and/or cathartic may be beneficial. Supportive care may include atropine sulfate for bradycardia, intravenous fluids and/or vasopressor agents for hypotension and vasodilators for hypertension. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression, hypotension and/or coma; blood pressure should be monitored since the administration of naloxone has occasionally resulted in paradoxical hypertension. Tolazoline administration has yielded inconsistent results and is not recommended as first-line therapy. Dialysis is not likely to significantly enhance the elimination of clonidine.

The largest overdose reported to date, involved a 28-year old male who ingested 100 mg of clonidine hydrochloride powder. This patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment. Plasma clonidine levels were 60 ng/mL after 1 hour, 190 ng/mL after 1.5 hours, 370 ng/mL after 2 hours, and 120 ng/mL after 5.5 and 6.5 hours. In mice and rats, the oral LD50 of clonidine is 206 and 465 mg/kg, respectively.

Dosage and Administration Apply Catapres-TTS (clonidine) once every 7 days to a hairless area of intact skin on the upper outer arm or chest. Each new application of Catapres-TTS should be on a different skin site from the previous location. If the system loosens during 7-day wearing, the adhesive overlay 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.

To initiate therapy, Catapres-TTS dosage should be titrated according to individual therapeutic requirements, starting with Catapres-TTS-1. If after one or two weeks the desired reduction in blood pressure is not achieved, increase the dosage by adding another Catapres-TTS-1 or changing to a larger system. An increase in dosage above two Catapres-TTS-3 is usually not associated with additional efficacy.

When substituting Catapres-TTS for oral clonidine or for other antihypertensive drugs, physicians should be aware that the antihypertensive effect of Catapres-TTS may not commence until 2-3 days after initial application. Therefore, gradual reduction of prior drug dosage is advised. Some or all previous antihypertensive treatment may have to be continued, particularly in patients with more severe forms of hypertension.

Renal Impairment Dosage must be adjusted according to the degree of impairment, and patients should be carefully monitored. Since only a minimal amount of clonidine is removed during routine hemodialysis, there is no need to give supplemental clonidine following dialysis.

HOW SUPPLIED Catapres-TTS-1 (clonidine) and Catapres-TTS-2 are supplied as 4 pouched systems and 4 adhesive overlays per carton, 3 cartons per shipper (NDC 0597-0031-12 and 0597-0032-12, respectively). Catapres-TTS-3 is supplied as 4 pouched systems and 4 adhesive overlays per carton (NDC 0597-0033-34). See chart below.

	Programmed Delivery Clonidine *in vivo* Per Day Over 1 Week	Clonidine Content	Size	Code
Catapres-TTS®-1 (clonidine)	0.1 mg	2.5 mg	3.5 cm^2	BI-31
Catapres-TTS®-2 (clonidine)	0.2 mg	5.0 mg	7.0 cm^2	BI-32
Catapres-TTS®-3 (clonidine)	0.3 mg	7.5 mg	10.5 cm^2	BI-33

STORAGE AND HANDLING Store below 86° F (30° C).

CAUTION Federal law prohibits dispensing without prescription.

Boehringer Ingelheim

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