

CLONIDINE - clonidine patch
Physicians Total Care, Inc.

Clonidine Transdermal System
(clonidine)

Clonidine Transdermal System 0.1 mg/day

Clonidine Transdermal System 0.2 mg/day

Clonidine Transdermal System 0.3 mg/day

Clonidine Transdermal System

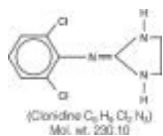
Formulated to deliver *in vivo* 0.1, 0.2, or
0.3 mg clonidine per day, for one week.

Rx only

Prescribing Information

DESCRIPTION

Clonidine Transdermal System is a transdermal system (patch) 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-imidazolidinylidenebenzenamine and has the following chemical structure:



System Structure and Components: Clonidine Transdermal System is a multi-laminate patch, 0.3 mm thick, containing clonidine as the active agent. The patch surface areas are 10.8 cm² (Clonidine Transdermal System 0.1 mg/day), 21.6 cm² (Clonidine Transdermal System 0.2 mg/day), and 32.4 cm² (Clonidine Transdermal System 0.3 mg/day). The composition per unit area is the same for all three doses.

Proceeding from the outer printed backing layer towards the surface applied to the skin, the system comprises: 1) a backing layer of polyethylene/aluminum/polyester film; 2) a drug reservoir layer of clonidine, isopropyl palmitate, and amine-compatible silicone adhesive; 3) an ethylene vinyl acetate (EVA) membrane that controls the rate of clonidine delivery from the system to the skin; 4) an amine-compatible silicone adhesive layer (ADHESIVE LAYER B); 5) an acrylate adhesive layer (ADHESIVE LAYER C) that attaches to the skin; and 6) a protective release liner of siliconized polyester that is removed prior to use.

Cross-sectional view of the Clonidine Transdermal System.

Not to scale.



Release Rate Concept: Clonidine Transdermal System is designed to deliver clonidine through the skin at an approximately constant rate for 7 days. Saturated clonidine in the reservoir layer provides a concentration gradient between the system and the skin. Clonidine diffuses from the higher concentration in the system to the lower concentration in the skin. The rate of delivery from the system is primarily controlled by passage of clonidine through the EVA membrane.

When a patch is applied to the skin (after removal of the protective release liner), clonidine dissolved in adhesive layers B & C is delivered to the skin. The EVA membrane then becomes the principal factor controlling clonidine delivery from the system by regulating clonidine release from the reservoir. A constant clonidine driving force is maintained by the drug reservoir layer, which contains a uniform dispersion of clonidine crystals. Clonidine is delivered through the skin and into the systemic circulation via the capillaries beneath the skin. Therapeutic plasma clonidine levels are achieved 2 to 3 days after initial application of Clonidine Transdermal System to the skin.

The 10.8, 21.6, and 32.4 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 Clonidine Transdermal System 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%-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

Clonidine Transdermal System is indicated in the treatment of hypertension. It may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

Clonidine Transdermal System should not be used in patients with known hypersensitivity to clonidine or to any other component of the transdermal 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 Clonidine Transdermal System, 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 Clonidine Transdermal System 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 Clonidine Transdermal System.

PRECAUTIONS

General: In patients who have developed localized contact sensitization to Clonidine Transdermal System continuation of Clonidine Transdermal System 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 Clonidine Transdermal System, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).

Clonidine Transdermal System 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 clonidine transdermal systems according to the instructions for use.

Perioperative Use: Clonidine Transdermal System 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 Clonidine Transdermal System 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 Clonidine Transdermal System (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 Clonidine Transdermal System 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 cover directly over the system to ensure adhesion during its 7-day use.

Used Clonidine Transdermal System 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 CLONIDINE TRANSDERMAL SYSTEM PATCHES OUT OF THE REACH OF CHILDREN. After use, Clonidine Transdermal System 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 Clonidine Transdermal System.

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 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 time 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 Clonidine Transdermal System 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**).

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

ADVERSE REACTIONS

Clinical trial experience with transdermal systems containing clonidine: Most systemic adverse effects during transdermal system therapy containing clonidine have been mild and have tended to diminish with continued therapy. In a 3-month multiclinic trial of clonidine transdermal therapy 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 cover throughout the 7-day dosage interval. Allergic contact sensitization to clonidine transdermal therapy 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 clonidine transdermal 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 clonidine transdermal treatment 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 transdermal systems containing clonidine: 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 hyperpigmentation.

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 Clonidine 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 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 phosphokinase, 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 Clonidine Transdermal 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 clonidine transdermal system 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 overdose. 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, semi-coma, 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 Clonidine Transdermal Systems once every 7 days to a hairless area of intact skin on the upper outer arm or chest. Each new application of Clonidine Transdermal System should be on a different skin site from the previous location. 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.

To initiate therapy, Clonidine Transdermal System dosage should be titrated according to individual therapeutic requirements, starting with Clonidine Transdermal System 0.1 mg. If after one or two weeks the desired reduction in blood pressure is not achieved, increase the dosage by adding another Clonidine Transdermal System 0.1 mg or changing to a larger system. An increase in dosage above two Clonidine Transdermal System 0.3 mg is usually not associated with additional efficacy.

When substituting Clonidine Transdermal System for oral clonidine or for other antihypertensive drugs, physicians should be aware that the antihypertensive effect of Clonidine Transdermal System 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

Clonidine Transdermal Systems 0.1 mg, Clonidine Transdermal Systems 0.2 mg, and Clonidine Transdermal Systems 0.3 mg are supplied as 4 pouched systems and 4 adhesive covers per carton.

	*Delivery Clonidine in vivo Per Day Over 1 Week	Clonidine Content	Size	Code	NDC Numbers
Clonidine Transdermal System	0.1 mg	3.67 mg	10.8 cm ²	Clonidine 0.1 mg	54868-6310-0
Clonidine Transdermal System	0.2 mg	7.34 mg	21.6 cm ²	Clonidine 0.2 mg	54868-6214-0
Clonidine Transdermal System	0.3 mg	11.02 mg	32.4 cm ²	Clonidine 0.3 mg	54868-6260-0

STORAGE AND HANDLING

Store at 20° to 25°C (68° to 77°F)

[see USP Controlled Room Temperature]

Manufactured by: AVEVA
Drug Delivery Systems
A Nitto Denko Company
Miramar, FL 33025

Manufactured for: **PAR PHARMACEUTICAL COMPANIES, INC.**
Spring Valley, NY 10977

3001690
OS774-86-1-06
Rev. 11/08

Relabeling of additional barcode by:

Physicians Total Care, Inc.
Tulsa, OK 74146

(Read the following instructions carefully before using this medication. If you have any questions, please consult with your doctor).

General Information

Clonidine Transdermal System is a tan colored, oval shaped adhesive PATCH containing an active blood-pressure-lowering medication. It is designed to deliver the drug into the body through the skin smoothly and consistently for one full week. Normal exposure to water, as in showering, bathing, and swimming, should not affect the PATCH.

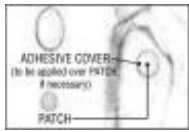


Figure 1:

The optional white, oval shaped, ADHESIVE COVER should be applied directly over the PATCH, should the PATCH begin to separate from the skin. The ADHESIVE COVER ensures that the PATCH sticks to the skin. The Clonidine Transdermal System PATCH must be replaced with a new one on a fresh skin site if the one in use significantly loosens or falls off.

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

How to Apply the Clonidine Transdermal System PATCH

1. Apply the tan colored, oval shaped Clonidine Transdermal System PATCH once a week, preferably at a convenient time on the same day of the week (i.e., prior to bedtime on Tuesday of week one; prior to bedtime on Tuesday of week two, etc.).

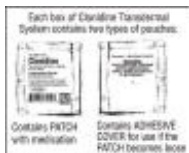


Figure 2:

2. Select a hairless area such as on the upper, outer arm or upper chest. The area chosen should be free of cuts, abrasions, irritation, scars or calluses and should not be shaved before applying the Clonidine Transdermal System PATCH. Do not place the Clonidine Transdermal System PATCH on skin folds or under tight undergarments, since premature loosening may occur.
3. Wash hands with soap and water and thoroughly dry them.
4. Clean the area chosen with soap and water. Rinse and wipe dry with a clean, dry tissue.
5. Select the pouch labeled Clonidine Transdermal System and open it as illustrated in *Figure 3*. Remove the tan colored, oval shaped PATCH from the pouch.



Figure 3:

6. Remove the white translucent plastic protective liner from the PATCH by gently peeling off one half of the liner at a time as shown in *Figure 4*. Avoid touching the sticky side of the Clonidine Transdermal System PATCH.

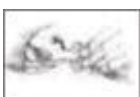


Figure 4:

7. Place the Clonidine Transdermal System PATCH on the prepared skin site (sticky side down) by applying firm pressure over the PATCH to ensure good contact with the skin, especially around the edges (*Figure 5*). Discard the white translucent plastic protective liner and wash your hands with

soap and water to remove any drug from your hands.



Figure 5:

8. After one week, remove the old PATCH and discard it (refer to **Instructions for Disposal**). After choosing a different skin site, repeat instructions 2 through 7 for the application of your next Clonidine Transdermal System PATCH.

What to do if your Clonidine Transdermal System PATCH becomes loose while wearing:

How to Apply the ADHESIVE COVER

Note: The white, oval shaped ADHESIVE COVER **does not contain any drug** and should not be used alone. The cover should be applied directly over the Clonidine Transdermal System PATCH **only** if the PATCH begins to separate from the skin, thereby ensuring that it sticks to the skin for seven full days.

1. Wash hands with soap and water and thoroughly dry them.
2. Using a clean, dry tissue, make sure that the area around the oval shaped, tan Clonidine Transdermal System PATCH is clean and dry. Press gently on the Clonidine Transdermal System PATCH to ensure that the edges are in good contact with the skin.
3. Take the white, oval shaped, ADHESIVE COVER (*Figure 6*) from the plain white pouch and remove the paper liner backing from the cover.



Figure 6:

4. Carefully center the white, oval shaped ADHESIVE COVER over the tan oval shaped, Clonidine Transdermal System PATCH and apply firm pressure, especially around the edges in contact with the skin.

Instructions for Disposal

KEEP OUT OF REACH OF CHILDREN

During or even after use, a PATCH contains active medication which may be harmful to infants and children if accidentally applied or ingested. After use, fold in half with the sticky sides together. Dispose of carefully out of reach of children.

Mfd by: AVEVA

Drug Delivery Systems, A Nitto Denko Company, Miramar, FL 33025

Mfd for: **PAR PHARMACEUTICAL COS, INC.**, Spring Valley, NY 10977

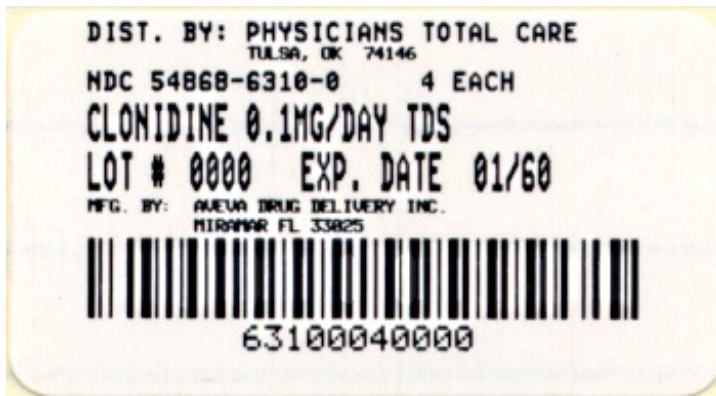
3001690

PI774-86-1-06

Rev. 11/08

Carton Label 0.1 mg

NDC 54868-6310-0



Clonidine

Transdermal System 0.1 mg/day

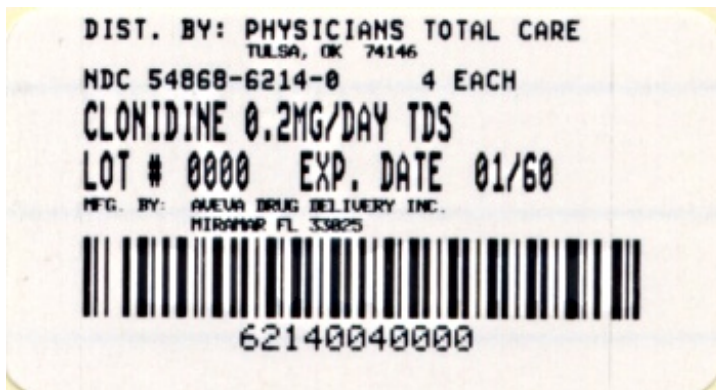
Rx only

4 Systems and 4 Adhesive Covers

0.1 mg

Carton Label 0.2 mg

NDC 54868-6214-0



Clonidine

Transdermal System 0.2 mg/day

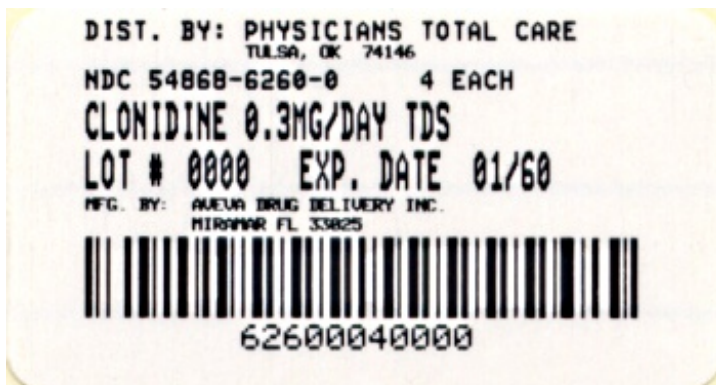
Rx only

4 Systems and 4 Adhesive Covers

0.2 mg

Carton Label 0.3 mg

NDC 54868-6260-0



Clonidine

Transdermal System 0.3 mg/day

Rx only

4 Systems and 4 Adhesive Covers

0.3 mg

CLONIDINE

clonidine patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-6310(NDC:49884-774)
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Clonidine (UNII: MN3L5RMN02) (Clonidine - UNII:MN3L5RMN02)	Clonidine	0.1 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
Isopropyl Palmitate (UNII: 8CRQ2TH63M)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6310-0	4 in 1 CARTON		
1		1 in 1 POUCH		
1		7 d in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076157	09/24/2011	

CLONIDINE

clonidine patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-6214(NDC:49884-775)
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Clonidine (UNII: MN3L5RMN02) (Clonidine - UNII:MN3L5RMN02)	Clonidine	0.2 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
Isopropyl Palmitate (UNII: 8CRQ2TH63M)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6214-0	4 in 1 CARTON		
1		1 in 1 POUCH		
1		7 d in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076157	12/14/2010	

CLONIDINE

clonidine patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:54868-6260(NDC:49884-776)
Route of Administration	TRANSDERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Clonidine (UNII: MN3L5RMN02) (Clonidine - UNII:MN3L5RMN02)	Clonidine	0.3 mg in 1 d

Inactive Ingredients

Ingredient Name	Strength
Isopropyl Palmitate (UNII: 8CRQ2TH63M)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:54868-6260-0	4 in 1 CARTON		
1		1 in 1 POUCH		
1		7 d in 1 PATCH		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076157	05/10/2011	

Labeler - Physicians Total Care, Inc. (194123980)

Establishment

Name	Address	ID/FEI	Business Operations
Physicians Total Care, Inc.		194123980	relabel, repack

Revised: 12/2011

Physicians Total Care, Inc.