Clonidine HCl
Clonipress®

75 mcg & 150 mcg Tablet

℞

Centrally Acting Antihypertensive / Alpha $_2$ Adrenoceptor Agonist

FORMULATION
Each tablet contains:
Clonidine HCl, USP ……..... 75 mcg or 150 mcg

PRODUCT DESCRIPTIONS
Clonipress® 75 mcg Tablet: White, round, 1/4" diameter, biconvex, plain tablet
Clonipress® 150 mcg Tablet: White, round, 5/16" diameter, flat, bisected on one side, plain on the other side

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Clonidine, an imidazoline derivative, is a central alpha-adrenergic stimulant that inhibits sympathetic cardio-accelerator and vasoconstrictor centers. Stimulation of alpha-adrenergic receptors in the brain stem results in reduced sympathetic outflow from the central nervous system (CNS) and a decrease in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged.

Clonidine lowers blood pressure to essentially the same extent in both supine and standing patients; thus, orthostatic effects are mild and infrequent. However, the underlying hemodynamic effects differ with the position of the patient. Administration of a single dose of clonidine to supine patients results in decreased cardiac output and stroke volume but total peripheral resistance remains unchanged. In patients in standing position or 45º tilt, a smaller decrease in cardiac output occurs and total peripheral resistance is decreased, but stroke volume is maintained. Prolonged therapy results in circulatory adjustments, so that the blood pressure lowering effect of clonidine largely results from reduced peripheral resistance. Rapid intravenous (IV), but not oral or intramuscular (IM), administration of clonidine produces direct stimulation of peripheral alpha$_2$-adrenergic receptors, resulting in transient vasoconstriction and an increase in systolic and diastolic blood pressure.

Blood pressure declines within 30 to 60 minutes after an oral clonidine dose, the maximum decrease occurring within 2 to 4 hours.

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

PHARMACOKINETICS
Clonidine is well absorbed from the gastrointestinal tract and does not exhibit a first pass effect. Peak plasma clonidine levels occur within 3 to 5 hours after oral dosing; plasma half-life is 12 to 16 hours and the elimination half-life is 6 to 24 hours.

Clonidine is rapidly and extensively distributed into tissues and crosses the blood brain barrier, as well as the placenta barrier. The plasma protein binding of clonidine is 30 to 40%.

Clonidine is metabolized in the liver. In humans, four metabolites have been detected but only one, the inactive p-hydroxyclonidine, has been identified.

The mean plasma half-life of clonidine is about 13 hours ranging between 10 to 20 hours in patients with normal renal function; the half-life increases up to 41 hours in patients with impaired renal function. About 40 to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 20% of the total dose is excreted with the feces.

The antihypertensive effect is reached at plasma clonidine concentrations between 0.2 and 1.5 ng/mL in patients with normal excretory functions. A further increase in the plasma levels will not enhance the antihypertensive effect.

Neither food nor the race of the patient influences the pharmacokinetics of clonidine.

INDICATION
Treatment of hypertension; may be used alone or concomitantly with other antihypertensives.

DOSAGE AND ADMINISTRATION
Individualize and adjust dose according to patient's blood pressure response and tolerance.

- ***Mild to moderate hypertension***
  - Initial Dose Orally, 75 to 150 mcg twice daily, in the morning and at bedtime
  - Dose may be increased in increments of 100 mcg/day until optimum response is achieved.
  - Maintenance Dose: Most common range is 200 to 600 mcg/day given in two divided doses
  - Maximum Dose: 2400 mcg/day in two to three divided doses
  - Sedative effects may be minimized by giving bulk of the daily dose at bedtime
- ***Severe hypertension***
  - Increase Initial dose to 300 mcg three times daily (900 mcg/day total loading dose)

Or, as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to clonidine or any component of the product
- Severe bradyarrhythmia resulting from either sick sinus syndrome or atrioventricular block of 2nd or 3rd degree

WARNINGS AND PRECAUTIONS
- ***Clonidine withdrawal:*** Instruct patients not to discontinue clonidine therapy without consulting a physician. Abrupt withdrawal of clonidine treatment may result in symptoms such as nervousness, agitation, headache, and tremor followed by a rapid increase in blood pressure and an increase in plasma catecholamine concentration. Such occurrences have usually been associated with previous administration of high oral doses (exceeding 1200 mcg/day) or with continuation of concomitant beta-blocker therapy. Rare cases of hypertensive encephalopathy, cerebrovascular accidents and death have been reported after clonidine withdrawal. When discontinuing therapy, clonidine dose should be reduced gradually over 2 to 4 days to avoid withdrawal symptoms.
- If clonidine therapy is to be discontinued in patients receiving clonidine and a beta-blocker concomitantly, the beta-blocker should be discontinued several days before clonidine therapy is discontinued.
- **Because children commonly have gastrointestinal illnesses that lead to vomiting, they may be particularly susceptible to hypertensive episodes resulting from abrupt inability to take medication.**
- **Perioperative use:** It is recommended that clonidine therapy not be interrupted for surgery; transdermal therapy may be continued throughout the perioperative period and oral therapy should be continued to within 4 hours before surgery. Blood pressure should be monitored carefully during surgery and additional measures to control blood pressure should be available if required. If clonidine therapy must be interrupted for surgery, parenteral antihypertensive therapy should be administered as necessary, and clonidine must be resumed as soon as possible.
- Use with caution in patients with severe coronary insufficiency, recent myocardial infarction, conduction disturbances, mild to moderate bradyarrhythmia (e.g., slow sinus rhythm), cerebrovascular disease, disorders of cerebral or peripheral perfusion, polyneuropathy, depression, chronic renal failure, Raynaud's disease, thromboangiitis obliterans, or constipation.
- As with other antihypertensive drugs, clonidine treatment should be monitored particularly carefully in patients with heart failure or severe coronary disease.
- No therapeutic effect of clonidine may be expected in hypertension caused by pheochromocytoma.
- The possibility that clonidine may lower blood pressure in patients receiving the drug for conditions other than hypertension (e.g., smoking cessation, pain management, attention deficit hyperactivity disorder) should be considered and blood pressure should be monitored as appropriate.
- Patients with a history of mental depression require careful supervision while receiving clonidine as they may be subject to further depressive episodes.
- Patients who engage in potentially hazardous activities such as operating machinery or driving should be warned of a possible sedative effect of clonidine. Patients should also be informed that this sedative effect may be increased by concomitant use of CNS depressants such as opiate agonists or other analgesics, barbiturates or other sedatives, anesthetics, or alcohol (see **Interactions with Other Medicaments**).
- In patients who have developed localized skin reaction to transdermal clonidine, substitution of oral clonidine may be associated with the development of a generalized rash.
- Patients who wear contact lenses should be warned that clonidine treatment may cause decreased lacrimation and dryness of the eyes.
- When clonidine is used off-label concomitantly with methylphenidate in children with attention-deficit hyperactivity disorder (ADHD), serious adverse reactions including death have been observed.

INTERACTIONS WITH OTHER MEDICAMENTS
CNS depressants (e.g., opiates), other analgesics, barbiturates or other sedatives, anesthetics, or alcohol: Clonidine may be additive with, or may potentiate the action of these drugs

Drugs that affect the sinus node function or atrioventricular nodal conduction (e.g., guanethidine), beta-blockers (e.g., propranolol), calcium antagonists, cardiac glycosides: Possible additive effects since clonidine may produce bradycardia and atrioventricular block

Haloperidol (high IV doses): In patients in a state of alcoholic delirium, high IV doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high IV doses of haloperidol. The causal relationship and relevance for antihypertensive treatment have not been established.

Psychotherapeutic agents, tricyclic antidepressants (e.g., imipramine, desipramine): May block the blood pressure lowering effect of clonidine. The increase in blood pressure usually occurs during the second week of tricyclic antidepressant therapy, but occasionally may occur during the first several days of concomitant therapy. Closely monitor blood pressure during the first several weeks of concurrent therapy and increase clonidine dosage to adequately control hypertension if necessary.

Drugs that increase blood pressure or induce sodium and water retention (e.g., Non-steroidal Anti-inflammatory Drugs, NSAIDs): May reduce the therapeutic effect of clonidine

Drugs with alpha$_2$-receptor blocking properties (e.g., phentolamine, tolazoline): May abolish the alpha2-receptor mediated effects of clonidine in a dose dependent manner

Other hypotensive agents: Increase blood pressure lowering effect of clonidine

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy: Pregnancy Category C. Clonidine should only be given during pregnancy if the benefit justifies any possible risk to the fetus. Careful monitoring of mother and child is recommended. Clonidine passes the placental barrier and may decrease the heart rate of the fetus. Post-partum, a transient increase in blood pressure in the newborn, cannot be excluded. If needed during pregnancy, the oral forms of clonidine should be preferred; the intravenous injection of clonidine should be avoided.
Lactation: Due to lack of information, clonidine is not recommended during breastfeeding.
Children: The safety and efficacy of clonidine in children and adolescents have not been established.

UNDESIRABLE EFFECTS
Cardiovascular: Atrioventricular block, bradyarrhythmia, bradycardia, chest pain, congestive heart failure, ECG abnormalities (e.g., arrhythmias, sinus node arrest, junctional bradycardia, conduction disturbances such as high degree atrioventricular block) manifested as Wenckebach period or ventricular trigeminy, flushes, hypotension, increases in blood pressure, orthostatic symptoms, palpitations, Raynaud's phenomenon, sinus bradycardia, syncope, tachycardia
Dermatologic: Alopecia, hair thinning, angioedema, hives, pruritus, rash, urticaria
Gastrointestinal: Abdominal pain, anorexia, constipation, dry mouth, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, vomiting
Genitourinary: Decreased sexual activity, difficulty in micturition, erectile dysfunction, impotence, loss of libido, nocturia, urinary retention
Hematologic: Thrombocytopenia
Hepatic: Hepatitis, mild transient abnormalities in liver function tests
Metabolic: Gynecomastia, transient elevation of blood glucose and serum creatine phosphokinase, transient hyperglycemia, weight gain
Musculoskeletal: Cramps of the lower limbs, fatigue, malaise, muscle or joint pain, weakness
Nervous: Agitation, anxiety, behavioral changes, cerebrovascular accidents, confusion, delirium, delusional perception, depression, dizziness, drowsiness, hallucinations (including visual and auditory), headache, insomnia, irritability, lethargy, localized numbness, mental depression, nervousness, nightmares, paresthesia, restlessness, sedation, sleep disorder, vivid dreams
Other adverse effects: Accommodation disorder; blurred vision; decreased lacrimation; dryness, itching or burning of eyes; dryness of the nasal mucosa; fever; increased sensitivity to alcohol; pallor; weakly positive Coombs' test; withdrawal syndrome

OVERDOSE AND TREATMENT
In a patient who ingested 100 mg clonidine, plasma levels were 60 ng/mL (1 hour), 190 ng/mL (1.5 hours), 370 ng/mL (2 hours) and 120 ng/mL (5.5 and 6.5 hours). The patient developed hypertension followed by hypotension, bradycardia, apnea, hallucinations, semicoma, and premature ventricular contractions. The patient fully recovered after intensive treatment.

Symptoms of clonidine overdosage are hypotension (which may be profound), transient hypertension, bradycardia, weakness, vomiting, irritability, diminished or absent reflexes, lethargy, somnolence, drowsiness, deep sedation, skin pallor, hypothermia, decreased or irregular heart rate, dryness of the mouth, constricted pupils with poor reaction to light, respiratory depression, hypoventilation, miosis, reversible cardiac conduction defects or dysrhythmias, apnea, coma, and seizures.

Induction of emesis is usually not recommended because of rapid onset of CNS depression. Establish respiration if necessary, perform gastric lavage and administer activated charcoal. A saline cathartic (magnesium sulfate) will increase the rate of transport through the gastrointestinal tract. Routine hemodialysis is of limited benefit because a maximum of 5% of circulating clonidine is removed.

Supportive care may include atropine sulfate for the treatment of persistent bradycardia, and dopamine infusion and IV fluids for hypotension.

Hypertension can be treated with IV furosemide or diazoxide or α-blocking agents such as phentolamine. Tolazoline, an alpha-blocker, in IV doses of 10 mg at 30 minute intervals may reverse clonidine's effects if other efforts fail. Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression, hypotension or coma.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help improve the safety of this medicine.

STORAGE CONDITION
Keep the product out of reach and sight of children
Store at temperatures not exceeding 30ºC

AVAILABILITY
Clonidine HCl (Clonipress®) 75 mcg Tablet, in blister pack by 20's (box of 100's)
Clonidine HCl (Clonipress®) 150 mcg Tablet, in blister pack by 20's (box of 100's)

CAUTION
Food, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Date of First Authorization: June 2012
Date of Revision of Package Insert: October 2011

REGISTRATION NUMBERS
Clonipress® 75 mcg Tablet: DRP-1868
Clonipress® 150 mcg Tablet: DRP-2046

Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
Distributed by **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines

P300000021570 Reg. IPOPHIL

UNILAB

Trusted Quality Healthcare