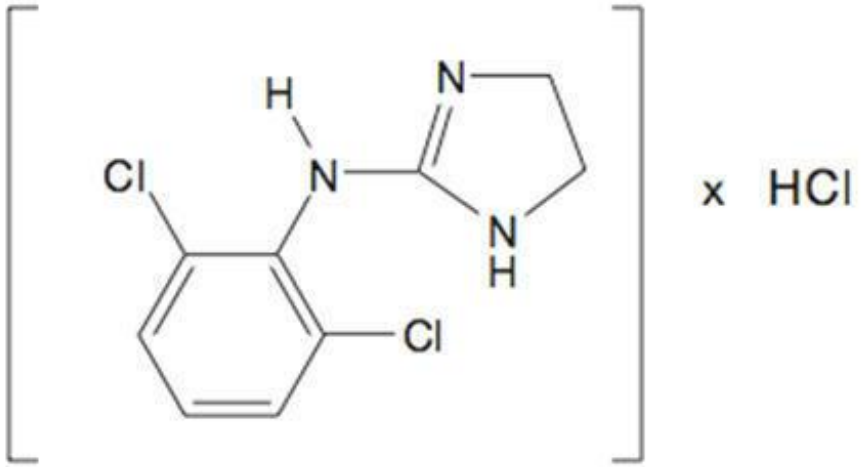
CLONIDINE HYDROCHLORIDE - clonidine hydrochloride tablet
REMEDYREPACK INC.

DESCRIPTION

Clonidine hydrochloride tablets USP is a centrally acting alpha-agonist hypotensive agent available as tablets for oral administration in three dosage strengths: 0.1 mg, 0.2 mg and 0.3 mg. The 0.1 mg tablet is equivalent to 0.087 mg of the free base.

Clonidine hydrochloride tablets USP contain the following inactive ingredients: lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate. The 0.1 mg also contains D&C yellow #10 aluminum lake, and the 0.3 mg contains D&C yellow #10 aluminum lake and FD&C blue #1 aluminum lake.

Clonidine hydrochloride is an imidazoline derivative and exists as a mesomeric compound. The chemical name is 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride. The following is the structural formula:



C9H9Cl2N3HCl Mol. Wt. 266.56

Clonidine hydrochloride is an odorless, bitter, white, crystalline substance soluble in water and alcohol.

CLINICAL PHARMACOLOGY

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 45tilt 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 response 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 growth hormone release in both children and adults, but does not produce a chronic elevation of growth hormone with long-term use.

PHARMACOKINETICS

The pharmacokinetics of clonidine is dose-proportional in the range of 100 to 600The absolute bioavailability of clonidine on oral administration is 70% to 80%. Peak plasma clonidine levels are attained in approximately 1 to 3 hours.
Following intravenous administration, clonidine displays biphasic disposition with a distribution half-life of about 20 minutes and an elimination half-life ranging from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Clonidine crosses the placental barrier. It has been shown to cross the blood-brain barrier in rats.
Following oral administration about 40% to 60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver. Neither food nor the race of the patient influences the pharmacokinetics of clonidine.
The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/mL in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.

INDICATIONS & USAGE

Clonidine hydrochloride tablets USP are indicated in the treatment of hypertension. Clonidine hydrochloride tablets USP may be employed alone or concomitantly with other antihypertensive agents.

CONTRAINDICATIONS

Clonidine hydrochloride tablets USP should not be used in patients with known hypersensitivity to clonidine (seePRECAUTIONS).

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 tremor 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 hydrochloride tablets USP, 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 hydrochloride tablets USP 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 hydrochloride tablets USP.
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.

PRECAUTIONS

General

In patients who have developed localized contact sensitization to clonidine-TTS, continuation of

clonidine-TTS or substitution of oral clonidine hydrochloride therapy may be associated with the development of a generalized skin rash.
In patients who develop an allergic reaction to clonidine-TTS, substitution of oral clonidine hydrochloride may also elicit an allergic reaction (including generalized rash, urticaria, or angioedema).
The sympatholytic action of clonidine may worsen sinus node dysfunction and atrioventricular (AV) block, especially in patients taking other sympatholytic drugs. There are post-marketing reports of patients with conduction abnormalities and/or taking other sympatholytic drugs who developed severe bradycardia requiring IV atropine, IV isoproterenol and temporary cardiac pacing while taking clonidine.
In hypertension caused by pheochromocytoma, no therapeutic effect of clonidine hydrochloride tablets USP can be expected.

Perioperative Use
Administration of clonidine hydrochloride tablets USP should be continued to within 4 hours of surgery and resumed as soon as possible thereafter. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required.

INFORMATION FOR PATIENTS
Patients should be cautioned against interruption of clonidine hydrochloride tablets USP therapy without their physician's advice.
Since patients may experience a possible sedative effect, dizziness, or accommodation disorder with use of clonidine, caution patients about engaging in activities such as driving a vehicle or operating appliances or machinery. Also, inform patients that this sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.
Patients who wear contact lenses should be cautioned that treatment with clonidine hydrochloride tablets USP may cause dryness of eyes.

DRUG INTERACTIONS
Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates or other sedating drugs. If a patient receiving clonidine hydrochloride is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose. If a patient receiving clonidine is also taking neuroleptics, orthostatic regulation disturbances (e.g., orthostatic hypotension, dizziness, fatigue) may be induced or exacerbated.
Monitor heart rate 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. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.
Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats (see Toxicology).
Based on observations in patients in a state of alcoholic delirium it has been suggested that high intravenous doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol. Causal relationship and relevance for clonidine oral tablets have not been established.

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 or 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 or female rats was unaffected by clonidine doses as high as 150(approximately 3 times MRDHD). In a separate experiment, fertility of female rats appeared to be affected at dose levels of 500 to 2000

PREGNANCY
Teratogenic Effects: Pregnancy Category C.

No adequate, well-controlled studies have been conducted in pregnant women. Clonidine crosses the placental barrier (seeCLINICAL PHARMACOLOGY, Pharmacokinetics). 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 hydrochloride is excreted in human milk, caution should be exercised when clonidine hydrochloride tablets USP are administered to a nursing woman.

PEDIATRIC USE
Safety and effectiveness in pediatric patients have not been established in adequate and well-controlled trials (seeWARNINGS, Withdrawal).

ADVERSE REACTIONS

The following less frequent adverse experiences have also been reported in patients receiving clonidine hydrochloride tablets USP, but in many cases patients were receiving concomitant medication and a causal relationship has not been established.
Body as a Whole:Fatigue, fever, headache, pallor, weakness, and withdrawal syndrome. Also reported were a weakly positive Coombs' test and increased sensitivity to alcohol.
Cardiovascular:Bradycardia, congestive heart failure, electrocardiographic abnormalities (i.e., sinus node arrest, junctional bradycardia, high degree AV block and arrhythmias), orthostatic symptoms, palpitations, Raynaud's phenomenon, syncope, and tachycardia. Cases of sinus bradycardia and atrioventricular block have been reported, both with and without the use of concomitant digitalis.
Central Nervous System:Agitation, anxiety, delirium, delusional perception, hallucinations (including visual and auditory), insomnia, mental depression, nervousness, other behavioral changes, paresthesia, restlessness, sleep disorder, and vivid dreams or nightmares.
Dermatological:Alopecia, angioneurotic edema, hives, pruritus, rash, and urticaria.
Gastrointestinal:Abdominal pain, anorexia, constipation, hepatitis, malaise, mild transient abnormalities in liver function tests, nausea, parotitis, pseudo-obstruction (including colonic pseudo-obstruction), salivary gland pain, and vomiting.

Genitourinary:Decreased sexual activity, difficulty in micturition, erectile dysfunction, loss of libido, nocturia, and urinary retention.
Hematologic:Thrombocytopenia.
Metabolic:Gynecomastia, transient elevation of blood glucose or serum creatine phosphokinase, and weight gain.
Musculoskeletal:Leg cramps and muscle or joint pain.
Oro-otolaryngeal:Dryness of the nasal mucosa.
Ophthalmological:Accommodation disorder, blurred vision, burning of the eyes, decreased lacrimation, and dryness of eyes.

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.

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 & ADMINISTRATION

Adults

The dose of clonidine hydrochloride tablets USP must be adjusted according to the patient's individual blood pressure response. The following is a general guide to its administration.

Initial Dose

0.1 mg tablet twice daily (morning and bedtime). Elderly patients may benefit from a lower initial dose.

Maintenance Dose

Further increments of 0.1 mg per day may be made at weekly intervals if necessary until the desired response is achieved. Taking the larger portion of the oral daily dose at bedtime may minimize transient adjustment effects of dry mouth and drowsiness. The therapeutic doses most commonly employed have ranged from 0.2 mg to 0.6 mg per day given in divided doses. Studies have indicated that 2.4 mg is the maximum effective daily dose, but doses as high as this have rarely been employed.

Renal Impairment

Patients with renal impairment may benefit from a lower initial dose. 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.

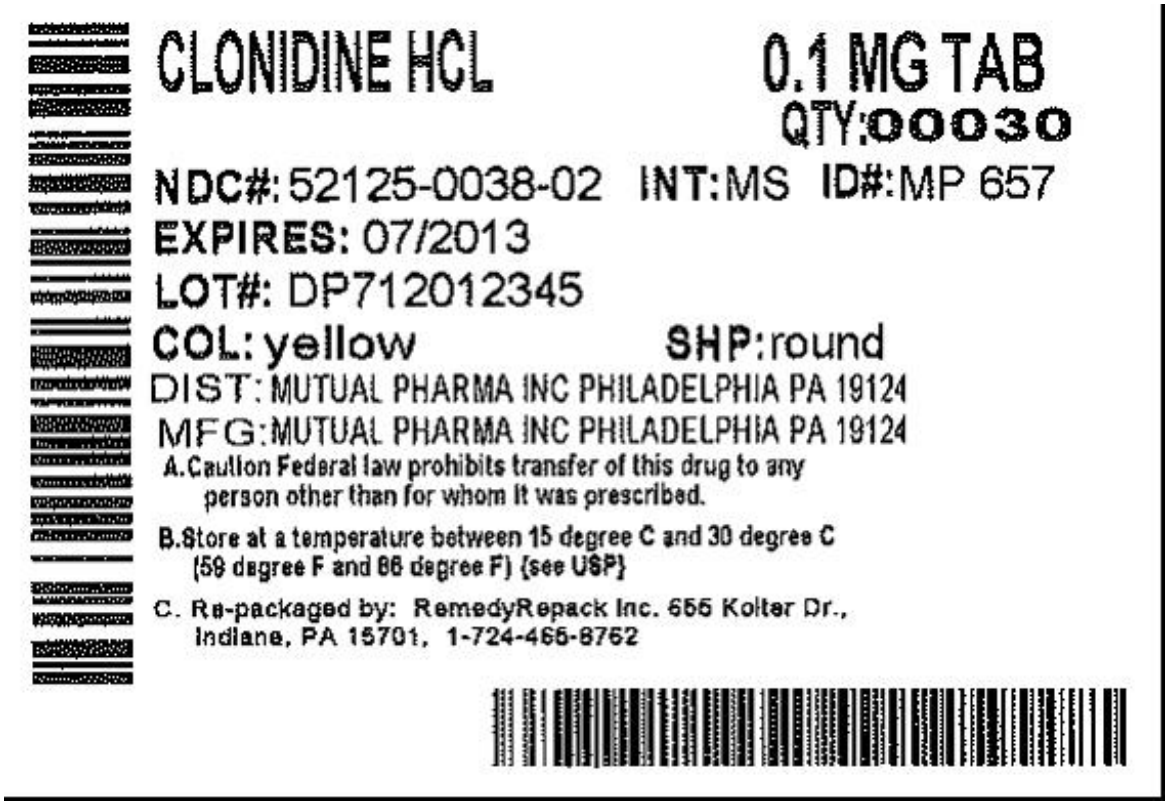
HOW SUPPLIED

Clonidine hydrochloride tablets USP are supplied as follows:
Clonidine hydrochloride tablets USP 0.1 mg, yellow, round, debossed MP 657 on one side and plain on the other side.
Bottles of 100NDC 53489-215-01Bottles of 1000NDC 53489-215-10Clonidine hydrochloride tablets USP 0.2 mg, white, round, debossed MP 658 on one side and plain on the other side.

Bottles of 100NDC 53489-216-01Bottles of 1000NDC 53489-216-10Clonidine hydrochloride tablets USP 0.3 mg, green, round, debossed MP 659 on one side and plain on the other side.
Bottles of 100NDC 53489-217-01

STORAGE AND HANDLING
Store at 20to 25(68to 77
[See USP Controlled Room Temperature]
DISPENSE IN TIGHT, LIGHT-RESISTANT CONTAINER.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION
DRUG: Clonidine Hydrochloride
GENERIC: clonidine hydrochloride
DOSAGE: TABLET
ADMINSTRATION: ORAL
NDC: 52125-038-02
STRENGTH:0.1 mg
COLOR: yellow
SHAPE: ROUND
SCORE: No score
SIZE: 7 mm
IMPRINT: 30
QTY: 30



CLONIDINE HYDROCHLORIDE

clonidine hydrochloride tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:52125-038(NDC:53489-215)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CLONIDINE HYDROCHLORIDE (UNII: W76I6XXF06) (CLONIDINE - UNII:MN3L5RMN02)	CLONIDINE HYDROCHLORIDE	0.1 mg

Inactive Ingredients

Ingredient Name	Strength
ALUMINUM OXIDE (UNII: LMI26O6933)	

CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
LACTOSE (UNII: J2B2A4N98G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	

Product Characteristics

Color	yellow	**Score**	no score
Shape	ROUND (TABLET)	**Size**	7mm
Flavor		**Imprint Code**	MP;657
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52125-038-02	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA070925	08/20/2012	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 8/2012 REMEDYREPACK INC.