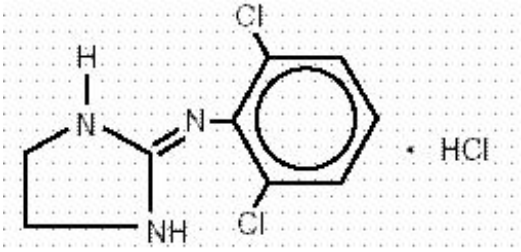
CLONIDINE HYDROCHLORIDE - clonidine hydrochloride tablet
State of Florida DOH Central Pharmacy

DESCRIPTION

Clonidine Hydrochloride 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.

The following inactive ingredients are contained in these products: corn starch, D and C yellow #10 Aluminum Lake, FD and C yellow #6 Aluminum Lake (Sunset Yellow Lake), lactose monohydrate, magnesium stearate, and sodium starch glycolate.

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:



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

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. Clonidine hydrochloride, acts relatively rapidly. The patient's blood pressure declines within 30 to 60 minutes after an oral dose, the maximum decrease occurring within 2 to 4 hours. 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 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 plasma level of clonidine peaks in approximately 3 to 5 hours and the plasma half-life ranges from 12 to 16 hours. The half-life increases up to 41 hours in patients with severe impairment of renal function. Following oral administration about 40-60% 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.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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, 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 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.

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.

ADVERSE REACTIONS

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, 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 atrioventricular 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 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.

There is no specific antidote for clonidine overdosage. Clonidine overdosage may result in the rapid development of CNS depression; therefore, induction of vomiting with ipecac syrup is not recommended. Gastric lavage may be indicated following recent and/or large ingestions. Administration of activated charcoal and/or a 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 LD_{50} of clonidine is 206 and 465 mg/kg, respectively.

DOSAGE AND ADMINISTRATION

Adults: The dose of clonidine hydrochloride 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: 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

0.1 mg — Each orange, round tablet imprinted with  and 127 on one side and bisect on the other side contains 0.1 mg of Clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2127-10) and 500 (NDC 0228-2127-50).

0.2 mg — Each orange, round tablet imprinted with  on one side and 128 and bisect on the other side contains 0.2 mg of Clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2128-10) and 500 (NDC 0228-2128-50).

0.3 mg — Each orange, round tablet imprinted with  on one side and 129 and bisect on the other side contains 0.3 mg of Clonidine hydrochloride USP and is supplied in bottles of 100 (NDC 0228-2129-10).

Dispense in a tight, light-resistant container as defined in the USP.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Manufactured by:
Actavis Elizabeth LLC
200 Elmora Avenue
Elizabeth, NJ 07207 USA

40-9009

Revised — January 2008

CLONIDINE HYDROCHLORIDE

clonidine hydrochloride tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:53808-0162(NDC:00228-2129-10)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CLONIDINE HYDROCHLORIDE (UNII: W76I6XXF06) (CLONIDINE - UNII:MN3L5RMN02)	CLONIDINE HYDROCHLORIDE	0.3 mg

Product Characteristics			
Color	orange	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	R127
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:53808-0162-1	30 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA070976	06/20/2009	

Labeler - State of Florida DOH Central Pharmacy (829348114)

Establishment

Name	Address	ID/FEI	Business Operations
State of Florida DOH Central Pharmacy		829348114	repack

Revised: 6/2009 State of Florida DOH Central Pharmacy