# CHLORDIAZEPOXIDE HYDROCHLORIDE- chlordiazepoxide hydrochloride capsule Cardinal Health

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#### CHLORDIAZEPOXIDE HYDROCHLORIDE CAPSULES USP CIV

Rx only

#### **DESCRIPTION**

Chlordiazepoxide hydrochloride is the prototype for the benzodiazepine compounds. It is a versatile therapeutic agent of proven value for the relief of anxiety. Chlordiazepoxide hydrochloride is among the safer of the effective psychopharmacologic compounds available, as demonstrated by extensive clinical evidence.

Chlordiazepoxide hydrochloride is 7-chloro-2- (methylamino)-5-phenyl-3*H*-1, 4-benzodiazepine 4-oxide hydrochloride. A white to practically white crystalline substance, it is soluble in water. It is unstable in solution and the powder must be protected from light. The structural formula is:

## $C_{16}H_{14}ClN_3O \cdot HCl M.W. 336.22$

Each capsule, for oral administration, contains either 5 mg, 10 mg or 25 mg of chlordiazepoxide hydrochloride USP and has the following inactive ingredients: anhydrous lactose, D&C yellow no. 10, FD&C blue no. 1, FD&C blue no. 1 aluminum lake, gelatin, hydrogenated vegetable oil, microcrystalline cellulose, pharmaceutical glaze, and titanium dioxide. The 5 mg and 25 mg also contains D&C yellow no. 10 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, propylene glycol, and synthetic black iron oxide. In addition, the 5 mg contains D&C red no. 33 and the 10 mg also contains butyl paraben, edetate calcium disodium, dimethyl polysiloxane, ethylene glycol monoethyl ether, FD&C red no. 40, methyl paraben, propyl paraben, sodium, sodium lauryl sulfate, sodium propionate, and soya lecithin.

#### CLINICAL PHARMACOLOGY

Chlordiazepoxide HCl has antianxiety, sedative, appetite-stimulating and weak analgesic actions. The precise mechanism of action is not known. The drug blocks EEG arousal from stimulation of the brain stem reticular formation. It takes several hours for peak blood levels to be reached and the half-life of the drug is between 24 and 48 hours. After the drug is discontinued plasma levels decline slowly over a period of several days. Chlordiazepoxide is excreted in the urine, with 1% to 2% unchanged and 3% to

6% as conjugate.

### Animal Pharmacology

The drug has been studied extensively in many species of animals and these studies are suggestive of action on the limbic system of the brain, which recent evidence indicates is involved in emotional responses.

Hostile monkeys were made tame by oral drug doses which did not cause sedation. Chlordiazepoxide HCl revealed a "taming" action with the elimination of fear and aggression. The taming effect of chlordiazepoxide HCl was further demonstrated in rats made vicious by lesions in the septal area of the brain. The drug dosage which effectively blocked the vicious reaction was well below the dose which caused sedation in these animals.

The LD<sub>50</sub> of parenterally administered chlordiazepoxide HCl was determined in mice (72 hours) and rats (5 days), and calculated according to the method of Miller and Tainter, with the following results: mice, IV,  $123 \pm 12$  mg/kg; mice, IM,  $366 \pm 7$  mg/kg; rats, IV,  $120 \pm 7$  mg/kg; rats, IM, > 160 mg/kg.

#### **Effects on Reproduction**

Reproduction studies in rats fed 10, 20 and 80 mg/kg daily and bred through one or two matings showed no congenital anomalies, nor were there adverse effects on lactation of the dams or growth of the newborn. However, in another study at 100 mg/kg daily there was noted a significant decrease in the fertilization rate and a marked decrease in the viability and body weight of off-spring which may be attributable to sedative activity, thus resulting in lack of interest in mating and lessened maternal nursing and care of the young. One neonate in each of the first and second matings in the rat reproduction study at the 100 mg/kg dose exhibited major skeletal defects. Further studies are in progress to determine the significance of these findings.

#### INDICATIONS AND USAGE

Chlordiazepoxide HCl capsules USP are indicated for the management of anxiety disorders or for the short term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The effectiveness of chlordiazepoxide HCl capsules USP in long term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

#### CONTRAINDICATIONS

Chlordiazepoxide HCl capsules are contraindicated in patients with known hypersensitivity to the drug.

#### **WARNINGS**

Chlordiazepoxide HCl may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. Similarly, it may impair mental alertness in children. The concomitant use of alcohol or other central nervous system depressants may have an additive effect. PATIENTS SHOULD BE WARNED ACCORDINGLY.

#### **Usage in Pregnancy**

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use

during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

#### **PRECAUTIONS**

In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or oversedation (10 mg or less per day initially, to be increased gradually as needed and tolerated). In general, the concomitant administration of chlordiazepoxide HCl and other psychotropic agents is not recommended. If such combination therapy seems indicated, careful consideration should be given to the pharmacology of the agents to be employed — particularly when the known potentiating compounds such as MAO inhibitors and phenothiazines are to be used. The usual precautions in treating patients with impaired renal or hepatic function should be observed.

Paradoxical reactions, e.g., excitement, stimulation and acute rage, have been reported in psychiatric patients and in hyperactive aggressive pediatric patients, and should be watched for during chlordiazepoxide HCl therapy. The usual precautions are indicated when chlordiazepoxide HCl is used in the treatment of anxiety states where there is any evidence of impending depression; it should be borne in mind that suicidal tendencies may be present and protective measures may be necessary. Although clinical studies have not established a cause and effect relationship, physicians should be aware that variable effects on blood coagulation have been reported very rarely in patients receiving oral anticoagulants and chlordiazepoxide HCl. In view of isolated reports associating chlordiazepoxide with exacerbation of porphyria, caution should be exercised in prescribing chlordiazepoxide to patients suffering from this disease.

#### Pediatric Use

Because of the varied response of pediatric patients to CNS-acting drugs, therapy should be initiated with the lowest dose and increased as required (see DOSAGE AND ADMINISTRATION). Since clinical experience with chlordiazepoxide HCl in pediatric patients under 6 years of age is limited, use in this age group is not recommended. Hyperactive aggressive pediatric patients should be monitored for paradoxical reactions to chlordiazepoxide HCl (see PRECAUTIONS).

#### **Information for Patients**

To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

#### ADVERSE REACTIONS

The necessity of discontinuing therapy because of undesirable effects has been rare. Drowsiness, ataxia and confusion have been reported in some patients — particularly the elderly and debilitated. While these effects can be avoided in almost all instances by proper dosage adjustment, they have occasionally been observed at the lower dosage ranges. In a few instances syncope has been reported.

Other adverse reactions reported during therapy include isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, as well as increased and decreased libido. Such side effects have been infrequent, and are generally controlled with reduction of dosage. Changes in EEG patterns (low-voltage fast activity) have been observed in patients during and after chlordiazepoxide HCl treatment.

Blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have occasionally been reported during therapy. When chlordiazepoxide HCl treatment is protracted, periodic blood counts and liver function tests are advisable.

#### DRUG ABUSE AND DEPENDENCE

Chlordiazepoxide hydrochloride capsules are classified by the Drug Enforcement Administration as a Schedule IV controlled substance.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have occurred following abrupt discontinuance of chlordiazepoxide. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving chlordiazepoxide or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

#### **OVERDOSAGE**

Manifestations of chlordiazepoxide overdosage includes somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal following chlordiazepoxide HCl overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of norepinephrine or metaraminol. Dialysis is of limited value. There have been occasional reports of excitation in patients following chlordiazepoxide HCl overdosage; if this occurs barbiturates should not be used. As with the management of intentional overdosage with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS, should be consulted prior to use.

#### DOSAGE AND ADMINISTRATION

Because of the wide range of clinical indications for chlordiazepoxide HCl, the optimum dosage varies with the diagnosis and response of the individual patient. The dosage, therefore, should be individualized for maximum beneficial effects.

ADULTS	USUAL DAILY DOSE
Relief of Mild and Moderate Anxiety Disorders and Symptoms of	5 mg or 10 mg, 3 or 4 times daily
Anxiety	
Relief of Severe Anxiety Disorders and Symptoms of Anxiety	20 mg or 25 mg, 3 or 4 times daily

### Preoperative Apprehension and Anxiety

On days preceding surgery, 5 to 10 mg orally, 3 or 4 times daily. If used as preoperative medication, 50 to 100 mg IM\* 1 hour prior to surgery.

#### PEDIATRIC PATIENTS

**USUAL DAILY DOSE** 

Because of the varied response of pediatric patients to CNS-acting drugs, 5 mg, 2 to 4 times daily therapy should be initiated with the lowest dose and increased as required. Since (may be increased in some clinical experience in pediatric patients under 6 years of age is limited, the use of pediatric patients to 10 mg, the drug in this age group is not recommended. 2 to 3 times daily)

For the relief of withdrawal symptoms of acute alcoholism, the parenteral form\* is usually used initially. If the drug is administered orally, the suggested initial dose is 50 to 100 mg, to be followed by repeated doses as needed until agitation is controlled — up to 300 mg per day. Dosage should then be reduced to maintenance levels.

\*See package insert for Injectable Chlordiazepoxide HCl.

#### **HOW SUPPLIED:**

Chlordiazepoxide Hydrochoride Capsules USP, 5 mg are available as a two-piece hard gelatin capsule with an aqua green opaque cap and a yellow opaque body filled with white powder, imprinted in black ink **barr** 158. They are available as follows:

NDC 51079-374-20 - Unit dose blister packages of 100 (10 cards of 10 capsules each).

Chlordiazepoxide Hydrochloride Capsules USP, 10 mg are available as a two-piece hard gelatin capsule with a black opaque cap and a green opaque body filled with white powder, imprinted in white ink **barr** 033. They are available as follows:

NDC 51079-375-20 - Unit dose blister packages of 100 (10 cards of 10 capsules each).

Chlordiazepoxide Hydrochloride Capsules USP, 25 mg are available as a two-piece hard gelatin capsule with an aqua green opaque cap and a white opaque body filled with white powder, imprinted in black ink **barr** 159. They are available as follows:

NDC 51079-141-20 - Unit dose blister packages of 100 (10 cards of 10 capsules each).

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature] in a dry place. Protect from light.

Manufactured by: Teva Pharmaceuticals USA Sellersville, PA 18960

Distributed by: UDL Laboratories, Inc. Rockford, IL 61103 S-2656 R16

6/12

### PRINCIPAL DISPLAY PANEL - 5 mg Bag

Chlordiazepoxide Hydrochloride Capsules, USP







# CHLORDIAZEPOXIDE HYDROCHLORIDE CAPSULES, USP 5 MG

10 CAPSULES

Each capsule contains 5 mg chlordiazepoxide hydrochloride, USP.

USUAL DOSAGE: See product insert for full prescribing information, precautions and warnings.

STORAGE: Store at 20 to 25 C (68 to 77 F) [See USP Controlled Room Temperature] in a dry place. Protect from light.

#### RX ONLY

WARNING: This package is intended for institutional use only. Keep this and all drugs out of the reach of children. This unit dose package is not child resistant.

NOTICE: Manufacturer's Name Changed

Manufactured by:
Teva Pharmaceuticals USA
Sellersville, PA 18960
Packaged and Distributed by:
UDL LABORATORIES, INC.
ROCKFORD, IL 61103
www.udllabs.com

Repackaged by Cardinal Health Zanesville, OH 43701 LC2598180611

LOT #: XXXX

EXP. DATE: 12/34

## PRINCIPAL DISPLAY PANEL - 10 mg Bag

Chlordiazepoxide Hydrochloride Capsules, USP

10 mg

10 Capsules







# CHLORDIAZEPOXIDE HYDROCHLORIDE CAPSULES, USP 10 MG

10 CAPSULES

Each capsule contains 10 mg chlordiazepoxide hydrochloride, USP

Usual Dosage: See product insert for prescribing information, precautions and warnings.

STORAGE: Store at 20 to 25 C (68 to 77 F). [See USP Controlled Room Temperature] in a dry place. Protect from light.

#### RX ONLY

WARNING: This package is intended for institutional use only. Keep this and all drugs out of the reach of children. This unit dose package is not child resistant.

Manufactured by. Teva Pharmaceuticals USA Sellersville, PA 18960

Packaged and Distributed by: UDL LABORATORIES, INC. ROCKFORD, IL 61103 www.udilabs.com

Repackaged by Cardinal Health Zanesville, OH 43701 LC2598260911

LOT #: XXXX

EXP. DATE: 12/34

### PRINCIPAL DISPLAY PANEL - 25 mg Bag

Chlordiazepoxide Hydrochloride Capsules, USP

25 mg

10 Capsules





NDC 55154-5652-0

# CHLORDIAZEPOXIDE HYDROCHLORIDE CAPSULES, USP 25 MG

10 CAPSULES

Each capsule contains 25 mg chlordiazepoxide hydrochloride, USP.

Usual Dosage: See product insert for prescribing information, precautions and warnings.

STORAGE: Store at 20 to 25 C (68 to 77 F). [See USP Controlled Room Temperature] in a dry place.

Protect from light.

#### RX ONLY

WARNING: This package is intended for institutional use only. Keep this and all drugs out of the reach of children. This unit dose package is not child resistant.

Manufactured by: Teva Pharmaceuticals USA Sellersville, PA 18960

Packaged and Distributed by:
Mylan Institutional Inc.
Rockford, IL 61103 U.S.A.
Mylan.com
Mylan is a trademark owned by its respective owner.
Repackaged by Cardinal Health
Zanesville, OH 43701
LC5118131013

LOT #: XXXX

EXP. DATE: 12/34

#### CHLORDIAZEPOXIDE HYDROCHLORIDE

chlordiazepoxide hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:55154- 5088(NDC:51079-374)
Route of Administration	ORAL	DEA Sche dule	CIV

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength

Inactive Ingredients			
Ingredient Name			
D&C YELLOW NO. 10			
FD&C BLUE NO. 1			
ALUMINUM O XIDE			
GELATIN			
ANHYDRO US LACTO SE			
CELLULO SE, MICRO CRYSTALLINE			
SHELLAC			
TITANIUM DIO XIDE			
D&C RED NO. 33			
FD&C BLUE NO. 2			
FD&C RED NO. 40			
PROPYLENE GLYCOL			
FERROSOFERRIC OXIDE			

Product Characteristics			
Color	GREEN (aqua green) , YELLOW	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	barr;158
Contains			

	Packaging			
:	# Item Code	Package Description	Marketing Start Date	Marketing End Date
	NDC:55154-5088-0	10 in 1 BAG		
	1	1 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA084768	0 4/0 1/20 11	

## CHLORDIAZEPOXIDE HYDROCHLORIDE

chlordiazepoxide hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:55154- 5089(NDC:51079-375)
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety			
Ingredient Name	Basis of Strength	Strength	
CHLORDIAZEPO XIDE HYDRO CHLORIDE (CHLORDIAZEPO XIDE)	CHLORDIAZEPOXIDE HYDROCHLORIDE	10 mg	

Inactive Ingredients			
Ingredient Name	Strength		
D&C YELLOW NO. 10			
FD&C BLUE NO. 1			
ALUMINUM O XIDE			
GELATIN			
ANHYDROUS LACTOSE			
CELLULO SE, MICRO CRYSTALLINE			
SHELLAC			
TITANIUM DIO XIDE			
BUTYLPARABEN			
DIMETHICONE			
ETHYLENE GLYCOL MONOETHYL ETHER			
FD&C RED NO. 40			
METHYLPARABEN			
PROPYLPARABEN			
SODIUM LAURYL SULFATE			
SO DIUM PRO PIO NATE			
LECITHIN, SO YBEAN			

Product Characteristics			
Color	BLACK, GREEN	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	barr;033
Contains			

Packaging			
# Item Code	Package Description	Marketing Start Date	Marketing End Date
1 NDC:55154-5089-0	10 in 1 BAG		
1	1 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA083116	0 4/0 1/20 11	

# CHLORDIAZEPOXIDE HYDROCHLORIDE

chlordiazepoxide hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	Item Code (Source)	NDC:55154- 5652(NDC:51079-141)
Route of Administration	ORAL	DEA Schedule	CIV

	Active Ingredient/Active Moiety			
l	Ingredient Name	Basis of Strength	Strength	
l	CHLORDIAZEPO XIDE HYDRO CHLORDIA (CHLORDIAZEPO XIDE)	CHLORDIAZEPOXIDE HYDROCHLORIDE	25 mg	

Inactive Ingredients			
Strength			

Product Characteristics			
Color	GREEN (aqua green) , WHITE	Score	no score
Shape	CAPSULE	Size	14mm
Flavor		Imprint Code	barr;159
Contains			

Packaging			
# Item Code	Package Description	<b>Marketing Start Date</b>	Marketing End Date
1 NDC:55154-5652-0	10 in 1 BAG		
1	1 in 1 BLISTER PACK		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA084769	04/01/2011	

# Labeler - Cardinal Health (188557102)

# Registrant - UDL Laboratories, Inc. (039615992)

Establishment			
Name	Address	ID/FEI	Business Operations
Cardinal Health		188557102	REPACK(55154-5088, 55154-5089, 55154-5652)

Revised: 11/2013 Cardinal Health