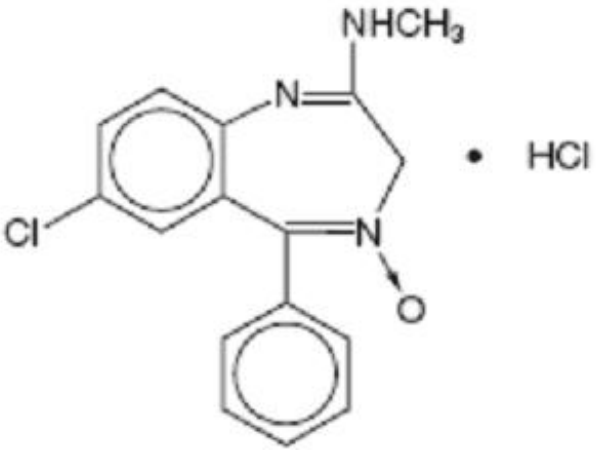
CHLORDIAZEPOXIDE HYDROCHLORIDE- chlordiazepoxide hydrochloride capsule
Bryant Ranch Prepack

CHLORDIAZEPOXIDE HYDROCHLORIDE CAPSULES, USP

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 HCl 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 of chlordiazepoxide hydrochloride is as follows:



$C_{16}H_{14}ClN_3O$ • HCl Molecular Weight: 336.22

Available as capsules for oral administration containing either 5 mg, 10 mg or 25 mg of chlordiazepoxide hydrochloride.

The inactive ingredients are as follows: D&C yellow no. 10, FD&C blue no. 1, FD&C blue no. 1 aluminum lake, gelatin, hydrogenated vegetable oil, lactose anhydrous, microcrystalline cellulose, pharmaceutical glaze, and titanium dioxide. The 5 mg also contains D&C red no. 33, 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. The 10 mg also contains butylparaben, calcium disodium, dimethyl polysiloxane, ethylene glycol monoethyl ether, FD&C red no. 40, methylparaben, pharmaceutical shellac, propylparaben, sodium, sodium lauryl sulfate, sodium propionate, and soya lecithin. The 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.

CLINICAL PHARMACOLOGY

Chlordiazepoxide HCI 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 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_{50} of parenterally administered chlordiazepoxide HCI 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 ± 12 mg/kg; mice, IM, 336 ± 7 mg/kg; rats, IV, 120 ± 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 HCI Capsules 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 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 HCI 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.

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 HCI 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 therapy. The usual precautions are indicated when chlordiazepoxide HCI capsules are 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. 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 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 (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 the 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 treatment.

Blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have occasionally been reported during therapy. When chlordiazepoxide 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 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, 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 Anxiety	5 mg or 10 mg, 3 or 4 times daily
Relief of Severe Anxiety Disorders and Symptoms of Anxiety	20 mg or 25 mg, 3 or 4 times daily
Geriatric Patients, or in the presence of debilitating disease	5 mg, 2 to 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* one hour prior to surgery.

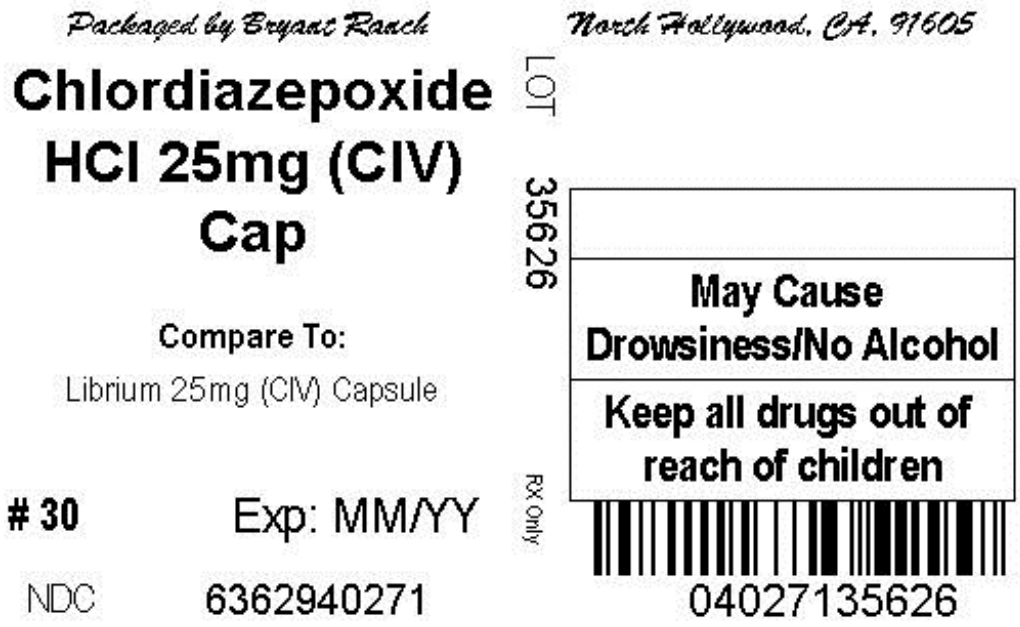
PEDIATRIC PATIENTS	*USUAL DAILY DOSAGE*
Because of the varied response of pediatric patients to CNS-acting drugs, therapy should be initiated with the lowest dose and increased as required. Since clinical experience in pediatric patients under 6 years of age is limited, the use of	*5 mg, 2 to 4 times daily (may be increased in some 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 Sterile Chlordiazepoxide Hydrochloride.

Chlordiazepoxide HCl 25mg (CIV) Cap



CHLORDIAZEPOXIDE HYDROCHLORIDE

chlordiazepoxide hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63629-4027(NDC:0555-0159)
Route of Administration	ORAL	**DEA Schedule**	CIV

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CHLORDIAZEPOXIDE HYDROCHLORIDE (UNII: MFM6K1XWDK) (CHLORDIAZEPOXIDE - UNII:6RZ6XEZ3CR)	CHLORDIAZEPOXIDE HYDROCHLORIDE	25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	

ALUMINUM OXIDE (UNII: LMI26O6933)	
GELATIN (UNII: 2G86QN327L)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
PROPYLENE GLYCOL (UNII: 6DC9Q167V3)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics

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

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63629-4027-1	30 in 1 BOTTLE		
2	NDC:63629-4027-2	25 in 1 BOTTLE		
3	NDC:63629-4027-3	10 in 1 BOTTLE		
4	NDC:63629-4027-4	20 in 1 BOTTLE		
5	NDC:63629-4027-5	15 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA084769	12/06/2010	

Labeler - Bryant Ranch Prepack (171714327)

Registrant - Bryant Ranch Prepack (171714327)

Establishment

Name	Address	ID/FEI	Business Operations
Bryant Ranch Prepack		171714327	REPACK(63629-4027) , RELABEL(63629-4027)