PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

CHLORDIAZEPOXIDE

Chlordiazepoxide hydrochloride

Capsule, 5 mg, 10 mg and 25 mg, Oral

USP

ATC Code: N05BA02

Anxiolytic

AA PHARMA INC.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CHLORDIAZEPOXIDE (chlordiazepoxide hydrochloride) is indicated:

- For the symptomatic relief of mild anxiety and tension, and for reduction of tension states that may accompany muscle spasm.
- As an adjunct in tension states associated with insomnia, pre- and post- operative apprehension, tension headache, premenstrual tension and stress, and functional gastrointestinal, cardiovascular, gynecological, and dermatological disorders with an emotional overlay.
- For the alleviation of alcohol withdrawal syndromes.
- To reduce anxiety associated with psychosis. Chlordiazepoxide should not be used in place of appropriate treatment in psychotic patients.

1.1 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for the pediatric population (see 4.2 Recommended Dose and Dosage Adjustment).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. See 7.1.4 Geriatrics.

Long-term use of CHLORDIAZEPOXIDE should be avoided in elderly patients. Enhanced monitoring is recommended. See 7 WARNINGS AND PRECAUTIONS, Falls and fractures; 4.1 Dosing considerations.

2 CONTRAINDICATIONS

CHLORDIAZEPOXIDE is contraindicated in:

- Patients who have known hypersensitivity to chlordiazepoxide or other benzodiazepines, or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with myasthenia gravis.
- Patients with acute narrow angle glaucoma.
- Patients with severe hepatic insufficiency.
- Patients with severe respiratory insufficiency (e.g. sleep apnea syndrome).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including CHLORDIAZEPOXIDE, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing CHLORDIAZEPOXIDE
- Monitor all patients regularly for the development of these behaviours or conditions.
- CHLORDIAZEPOXIDE should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like CHLORDIAZEPOXIDE, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of CHLORDIAZEPOXIDE.
- Terminate treatment with CHLORDIAZEPOXIDE by gradually tapering the dosage schedule under close monitoring.

See 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance.

Risks from Concomitant use with Opioids

Concomitant use of CHLORDIAZEPOXIDE and opioids may result in profound sedation, respiratory depression, coma and death. See 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- CHLORDIAZEPOXIDE should always be prescribed at the lowest effective dose for the shortest duration possible.

Discontinuation

CHLORDIAZEPOXIDE can produce withdrawal signs and symptoms or rebound phenomena following

abrupt discontinuation or rapid dose reduction. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal, 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.

Geriatric
Geriatric patients in particular may be more sensitive to benzodiazepines. See 7 WARNINGS AND PRECAUTIONS, Falls and Fractures. Long-term use of CHLORDIAZEPOXIDE should be avoided in elderly patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adults: Usually 15 to 40 mg daily in divided doses. In severe cases 25 mg 3 or 4 times daily may be given.

Elderly or debilitated patients: 5 mg 2 to 4 times daily.

Preoperative apprehension: 5 to 10 mg 3 to 4 times daily on days prior to surgery.

Pediatrics: Initiate therapy with 5 to 10 mg daily in divided doses, increasing, if necessary, to 30 mg daily in divided doses 2 to 3 times daily.

4.4 Administration

CHLORDIAZEPOXIDE capsules should be swallowed whole with a glass of water.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5 OVERDOSAGE

Manifestations of chlordiazepoxide hydrochloride overdosage include drowsiness, ataxia and confusion. Depression of the cardiovascular and respiratory centers may occur. In children, induce emesis. Management consists of supportive measures, close supervision and monitoring. Cardiovascular and CNS stimulants may be used if necessary. Dialysis appears to be of little value. There have been occasional reports of excitation in patients following chlordiazepoxide hydrochloride 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsule 5mg, 10 mg and 25 mg of chlordiazepoxide hydrochloride	Each capsule contains the non-medicinal ingredients cornstarch, lactose monohydrate, stearic acid and talc. The capsule shell ingredients include D&C yellow #10, FD&C blue #1 (10 mg only), FD&C green #3, **FD&C red #40 (10 mg only),** FD&C yellow #6, gelatin, and titanium dioxide. The edible black ink used for imprinting on the 5 mg and 25 mg capsules contains the non-medicinal ingredients allura red AC aluminum lake, black iron oxide, brilliant blue FCF aluminum lake, D&C yellow #10 aluminum lake, indigo carmine aluminum lake, propylene glycol and shellac glaze. The edible white ink used for imprinting on the 10 mg capsule contains the non-medicinal ingredients ammonium hydroxide, propylene glycol, shellac glaze, simethicone, and titanium dioxide.

Each yellow opaque body and light green opaque cap, hard gelatin capsule, imprinted 5 in black ink with a white powder fill, contains 5 mg chlordiazepoxide hydrochloride.

Each light green opaque body and black cap, hard gelatin capsule, imprinted 10 in white ink with a white powder fill, contains 10 mg chlordiazepoxide hydrochloride.

Each white opaque body and light green opaque cap, hard gelatin capsule, imprinted 25 in black ink with a white power fill, contains 25 mg chlordiazepoxide hydrochloride.

Each strength is available in package size of 100 capsules.

7 WARNINGS AND PRECAUTIONS

General

Concomitant use with opioids: Concomitant use of benzodiazepines, including CHLORDIAZEPOXIDE, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from

Concomitant with Opioids, 9.1 Serious Drug Interactions.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe CHLORDIAZEPOXIDE concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of CHLORDIAZEPOXIDE than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking CHLORDIAZEPOXIDE, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. See 5 OVERDOSAGE.

Advise both patients and caregivers about the risks of respiratory depression and sedation when CHLORDIAZEPOXIDE is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

Dependence/Tolerance

Use of benzodiazepines, such as CHLORDIAZEPOXIDE, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with CHLORDIAZEPOXIDE with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing CHLORDIAZEPOXIDE. In individuals prone to substance use disorder, CHLORDIAZEPOXIDE should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- CHLORDIAZEPOXIDE should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal

Benzodiazepines, such as CHLORDIAZEPOXIDE, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk

of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia, a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, on withdrawal of treatment.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; 4.1 Dosing Considerations.

Driving and Operating Machinery

Patients receiving CHLORDIAZEPOXIDE should be cautioned against engaging in hazardous activities requiring complete mental alertness, judgement and physical coordination, such as driving an automobile or operating dangerous machinery.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Hematologic

Leucopenia and rare cases of agranulocytosis have been reported (see 8.1 Adverse Reaction Overview). CHLORDIAZEPOXIDE should be administered with caution to patients with a history of blood dyscrasias.

Hepatic/Biliary/Pancreatic

CHLORDIAZEPOXIDE is contraindicated in patients with severe hepatic insufficiency (see 2 CONTRAINDICATIONS).

Hepatic dysfunction and jaundice have occasionally been reported (see 8.1 Adverse Reaction Overview). CHLORDIAZEPOXIDE should be administered with caution to patients with history of hepatic disease.

Monitoring and Laboratory Tests

Periodic blood counts and liver function tests are recommended if the medication is administered over a protracted period of time.

Neurologic

Memory disturbance

Anterograde amnesia may occur with therapeutic doses of benzodiazepines and may be associated with inappropriate behaviour. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Psychiatric

Confusion

Benzodiazepines affect mental efficiency, e.g. concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Confusion has been reported with CHLORDIAZEPOXIDE (see 8.1 Adverse Reaction Overview).

Mental and Emotional Disorders

Caution should be exercised if CHLORDIAZEPOXIDE is prescribed to patients with signs or symptoms of depression that could be intensified by benzodiazepines. The potential for self-harm is high in patients with depression. Employ the usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary.

Paradoxical Reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects may occur due to chlordiazepoxide in rare instances and in random fashion (see 8.1 Adverse Reaction Overview). These reactions are more likely to occur in children and in the elderly. Should this occur, the use of chlordiazepoxide should be discontinued.
Since excitement and other paradoxical reactions can result from the use of anxiolytic sedatives in psychotic patients, chlordiazepoxide should not be used in ambulatory patients suspected of having psychotic tendencies.
These reactions may be secondary to the relief of anxiety symptoms and should be watched for particularly in the early phase of medication.

Renal

CHLORDIAZEPOXIDE should be administered with caution to patients with history of renal disease.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

  Teratogenic and non-teratogenic effects have been reported in association to use of benzodiazepines during pregnancy. The use of CHLORDIAZEPOXIDE during pregnancy is not recommended (see 7.1.1 Pregnant Women).

7.1 Special Populations

7.1.1 Pregnant Women

Chlordiazepoxide crosses the placental barrier (see 10.3 Pharmacokinetics).

Several studies have suggested an increased risk of congenital malformations (e.g. congenital malformations of the heart, cleft lip and/or palate) associated with the use of diazepam, chlordiazepoxide and meprobamate during the first trimester of pregnancy. Therefore, the administration of chlordiazepoxide is rarely justified in women of childbearing potential. If the drug is prescribed for a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become, or suspects that she is pregnant.

Chronic use of chlordiazepoxide during pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery. Use of chlordiazepoxide just prior to or during labour may cause neonatal flaccidity.

7.1.2 Breast-feeding

Chlordiazepoxide or its metabolites may be excreted in breast milk. Therefore, it should not be administered to breast-feeding women, unless the expected benefit to the mother outweighs the potential risk to the infant.
Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for the pediatric population (see 4.2 Recommended Dose and Dosage Adjustment).

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Caution should be exercised and the minimal effective dosage that does not cause ataxia or over-sedation should be maintained in elderly or debilitated patients. Dosage should be increased gradually as needed and tolerated. See 4 DOSAGE AND ADMINISTRATION.

Long-term use of CHLORDIAZEPOXIDE should be avoided in elderly or debilitated patients who may be

more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions have been reported with chlordiazepoxide:

Blood and lymphatic system disorders: dyscrasias including agranulocytosis, leucopenia

Gastrointestinal disorders: nausea, constipation

Hepatobiliary disorders: jaundice, hepatic dysfunction

Immune system disorders: edema

Nervous system disorders:

- Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by the proper dosage adjustment, but are also occasionally observed at the lower dosage ranges.
- Syncope
- Extrapyramidal symptoms
- Changes in electroencephalogram (EEG) patterns (low voltage fast activity) may appear during and after treatment.

Psychiatric disorders: Paradoxical reactions such as excitement, stimulation, elevation of mood and rage.

Reproductive system and breast disorders: Increased and decreased libido, minor menstrual irregularities

Skin and subcutaneous disorders: skin eruptions

8.5 Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications

There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal

Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as CHLORDIAZEPOXIDE. Severe and life-threatening symptoms have been reported. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of CHLORDIAZEPOXIDE and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

See 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids

9.2 Drug Interactions Overview

CHLORDIAZEPOXIDE may produce additive CNS depressant effects when co- administered with alcohol, sedative antihistamines, narcotic analgesics, anticonvulsants, or psychotropic medications which themselves can produce CNS depression.

The activity of benzodiazepines, including CHLORDIAZEPOXIDE, may be enhanced by compounds which inhibit certain hepatic enzymes such as cytochrome P450 enzymes. Examples include cimetidine or erythromycin.

9.3 Drug-Behavioural Interactions

CHLORDIAZEPOXIDE may produce additive CNS depressant effects when co-administered with alcohol.

Patients should also be warned against the ingestion of alcohol, since tolerance may be decreased and effects enhanced.

9.4 Drug-Drug Interactions

CNS depressant drugs

Benzodiazepines, including CHLORDIAZEPOXIDE, may produce additive CNS depressant effects when co-administered sedative antihistamines, narcotic analgesics, anticonvulsants, antipsychotics (neuroleptics), anesthetics, antidepressant agents or psychotropic medications (e.g. monoamine oxidase inhibitors and phenothiazines) which themselves can produce CNS depression.

Cytochrome P450

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Examples include cimetidine or erythromycin.

Opioids

Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including CHLORDIAZEPOXIDE, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory

depression and sedation (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

Oral anticoagulants

Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; a causal relationship has not been established clinically.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Chlordiazepoxide depresses the CNS at the levels of the cortex, the limbic system, and the brain stem reticular formation, and also depresses polysynaptic reflex arcs of the spinal cord. It does not produce ganglionic blockade or reduce affective responses at therapeutic dosage as do phenothiazine drugs and reserpine; its skeletal muscle relaxant properties are similar to those of meprobamate. Amine oxidase inhibition has not been demonstrated with chlordiazepoxide.

10.2 Pharmacodynamics

There is no relevant data available on the pharmacodynamic effect of CHLORDIAZEPOXIDE in humans.

10.3 Pharmacokinetics

Absorption

Following oral administration, the drug appears in the blood stream in 0.5 to 1 hour, peak blood levels occur in 2 to 4 hours. After i.m. administration, effects of the drug appear in 15 to 30 minutes.

In humans, the plasma half-life of a single oral dose of chlordiazepoxide is about 20 to 24 hours.

Distribution:

There is no relevant distribution data available for CHLORDIAZEPOXIDE in humans.

Following administration of radioactive chlordiazepoxide to rats, distribution of the drug or its metabolites has been shown to be fairly even throughout all body tissues.

Metabolism:

The drug is metabolized, presumable by the liver, to a lactam derivative, which may be further metabolized to the amino acid N-(2-amino-5-chloroalpha-phenylbenzylidine)-glycine-N-oxide.

Elimination

Chlordiazepoxide is excreted, chiefly as the lactam derivative, as the amino acid and conjugates of the amino acid, in the urine and feces.

Special Populations and Conditions

- **Pregnancy and Breast-feeding**: Chlordiazepoxide readily passes the placental barrier, with the concentration of the drug in the fetal circulation approaching or equaling that in maternal circulation.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C – 30°C).

CHLORDIAZEPOXIDE should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

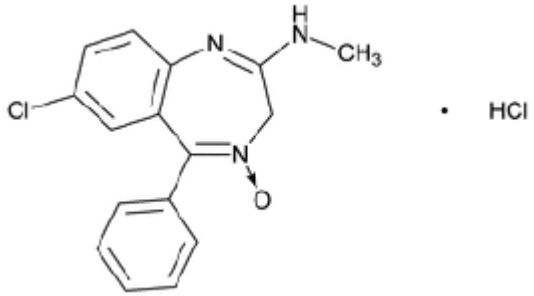
12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Chlordiazepoxide hydrochloride
Chemical name:	*3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide, monohydrochloride.* *7-Chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide monohydrochloride.*
Molecular formula and molecular mass:	$C_{16}H_{14}ClN_3O$ and 336.22 g/mol
Structural formula:	
Physicochemical properties:	White or practically white, odorless, crystalline powder with a melting point 236-236.5 °C. Soluble in water; sparingly soluble in alcohol; insoluble in solvent hexane, pK 4.8.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Information is not available.

Carcinogenicity: No long-term animal studies have been performed to evaluate carcinogenic potential.

Genotoxicity: No long-term animal studies have been performed to evaluate mutagenic potential.

Reproductive and Developmental Toxicology: No long-term animal studies have been performed to evaluate whether CHLORDIAZEPOXIDE affects fertility in males or females.

Special Toxicology: Information is not available.

Juvenile Toxicity: Information is not available.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrCHLORDIAZEPOXIDE

Chlordiazepoxide Hydrochloride Capsules USP

Read this carefully before you start taking **CHLORDIAZEPOXIDE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CHLORDIAZEPOXIDE**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take CHLORDIAZEPOXIDE exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take CHLORDIAZEPOXIDE with:

- **opioids**
- **alcohol or**
- **illicit drugs**

Your healthcare professional should:

- **talk to you about the risks of treatment with CHLORDIAZEPOXIDE as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing CHLORDIAZEPOXIDE**
- **monitor you while you are taking CHLORDIAZEPOXIDE for the signs and symptoms of misuse and abuse. If you feel like you are craving CHLORDIAZEPOXIDE, or not using it as directed, talk to your doctor right away.**

Store CHLORDIAZEPOXIDE in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking CHLORDIAZEPOXIDE, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)

- **Always contact your doctor before stopping, or lowering your dose of CHLORDIAZEPOXIDE or changing your medicine.**

CHLORDIAZEPOXIDE with Opioids: Taking CHLORDIAZEPOXIDE with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**
- **coma**
- **death**

What is CHLORDIAZEPOXIDE used for?

CHLORDIAZEPOXIDE is used to treat:

- the symptoms of mild anxiety and tension
- tension associated from muscle pain
- the symptoms of alcohol withdrawal
- anxiety associated with mental health problems.

CHLORDIAZEPOXIDE is also used as a supportive treatment to relieve tension associated with:

- insomnia,
- anxiety before and after surgery,
- tension headaches,
- premenstrual tension and stress, and
- anxiety and stress from digestive, heart, reproductive and skin disorders.

If you are 65 years or older, talk to your doctor before starting CHLORDIAZEPOXIDE. CHLORDIAZEPOXIDE may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does CHLORDIAZEPOXIDE work?

Chlordiazepoxide belongs to a group of medicines called benzodiazepines. These medicines work by changing the chemical activity in the brain to reduce anxiety and worry. Chlordiazepoxide relieves pain by relaxing your muscles.

What are the ingredients in CHLORDIAZEPOXIDE?

Medicinal ingredients: chlordiazepoxide hydrochloride

Non-medicinal ingredients: cornstarch, lactose monohydrate, stearic acid and talc.

The capsule shell ingredients include: D&C yellow #10, FD&C blue #1 (10 mg only), FD&C green #3, FD&C red #40 (10 mg only), FD&C yellow #6, gelatin, and titanium dioxide.

The ink used for imprinting on the 5 mg and 25 mg capsules includes: allura red AC aluminum lake, black iron oxide, brilliant blue FCF aluminum lake, D&C yellow #10 aluminum lake, indigo carmine aluminum lake, propylene glycol and shellac glaze.

The ink used for imprinting on the 10 mg capsule includes: ammonium hydroxide, propylene glycol, shellac glaze, simethicone, and titanium dioxide.

CHLORDIAZEPOXIDE comes in the following dosage forms:

Capsules: 5 mg, 10 mg and 25 mg.

Do not use CHLORDIAZEPOXIDE if:

- you are allergic to chlordiazepoxide hydrochloride or any of the other ingredients in CHLORDIAZEPOXIDE;
- you have myasthenia gravis (a disease that causes weakness in your muscles)
- you have acute narrow angle glaucoma;
- you have severe liver problems;

- you have severe lung or breathing problems such as sleep apnea syndrome.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CHLORDIAZEPOXIDE. Talk about any health conditions or problems you may have, including if you:

- have a blood disease or disorder (blood dyscrasias),
- have liver or kidney problems,
- are 65 years of age or older,
- have a history of depression, mental health problems, or suicidal thoughts,
- are pregnant, think you may be pregnant or planning to become pregnant,
- are breastfeeding or planning to breastfeed,
- have ever had a problem with:
  - substance use, including prescribed or illegal drugs, or
  - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness),
- are allergic to lactose.

Other warnings you should know about:

Driving and using machines: CHLORDIAZEPOXIDE may affect your ability to be alert. Do not drive or use machinery while you are taking CHLORDIAZEPOXIDE until you know how it affects you.

Monitoring and Tests: During your treatment with CHLORDIAZEPOXIDE, your healthcare professional may do test including tests to monitor your blood counts and your liver function.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop CHLORDIAZEPOXIDE.

Your risk of going through withdrawal is higher if you are taking CHLORDIAZEPOXIDE for a long time or at high doses. However, symptoms can still occur if you are taking CHLORDIAZEPOXIDE as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)

- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always contact your doctor before stopping or reducing your dose of CHLORDIAZEPOXIDE or changing medications
- always follow your doctor's instructions on how to reduce your dose carefully and safely
- tell your doctor **right away** if you experience any unusual symptoms after changing or stopping your treatment

CHLORDIAZEPOXIDE with Opioids: Taking CHLORDIAZEPOXIDE with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking CHLORDIAZEPOXIDE

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and CHLORDIAZEPOXIDE affects you.

Falls and Fractures: Benzodiazepines like CHLORDIAZEPOXIDE can cause you to feel sleepy, dizzy and affect your balance. This increases your risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

Memory problems: CHLORDIAZEPOXIDE can cause a type of memory loss known as amnesia. This is more common in elderly patients.

Mental and behavioural changes: Changes in thinking and behaviour may happen when you take CHLORDIAZEPOXIDE. Some of these changes include:

- aggressiveness,
- irritability,
- anxiety,
- restlessness,
- delusions,
- hallucinations and

- feeling like you are not yourself.

This is more common in elderly patients. If you develop any unusual thoughts or behaviour while taking CHLORDIAZEPOXIDE, tell your healthcare professional right away.

Pregnancy and breastfeeding: Benzodiazepines, such as CHLORDIAZEPOXIDE, may harm your unborn baby if you are pregnant. It may also cause side effects and withdrawal symptoms in your baby after birth. This risk is higher during the first trimester or last weeks of pregnancy. If you are able to get pregnant, want to be or think you are pregnant, there are specific risks you should discuss with your healthcare professional. CHLORDIAZEPOXIDE may cause unwanted side effects to your baby if you take it while breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CHLORDIAZEPOXIDE:

Serious Drug Interactions

Taking CHLORDIAZEPOXIDE and opioids may cause:

- **severe drowsiness**
- **trouble breathing**
- **coma**
- **death**

- alcohol. Do not take CHLORDIAZEPOXIDE if you drink alcohol;
- oral anticoagulants used to thin the blood;
- sedative antihistamines that are used to treat allergies;
- medicines used to treat mental health disorders (antipsychotics and psychotropic medications) such as phenothiazines;
- antidepressants used to treat depression such as monoamine inhibitors;
- anticonvulsants used to prevent or treat seizures;
- anesthetics used during surgery;
- medicines that inhibit certain liver enzymes, particularly cytochrome P450 (such as cimetidine and erythromycin). If you are unsure, talk to your healthcare professional.

How to take CHLORDIAZEPOXIDE:

- Take CHLORDIAZEPOXIDE exactly as your healthcare professional tells you to take it.
- Swallow the capsule whole with a glass of water.

Usual dose:

Your healthcare professional will decide on the dose that is best for you. Based on how you respond and how you tolerate your medicine, your healthcare professional may change your dose.

Adults: 15 to 40 mg daily in divided doses. In severe cases 25 mg 3 or 4 times daily may be given.

Elderly or weakened patients: 5 mg, taken 2 to 4 times daily.

Before surgery: 5 to 10 mg taken 3 to 4 times daily on days prior to surgery.

Children: Start with 5 to 10 mg daily in divided doses. Your healthcare professional will increase the dose if required to 30 mg daily in 2 to 3 divided doses.

Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Overdose:

Some of the signs of an overdose include drowsiness, ataxia (unsteadiness and clumsiness), and confusion.

If you think you, or a person you are caring for, have taken too much CHLORDIAZEPOXIDE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss a dose of CHLORDIAZEPOXIDE, do not take the missed dose. Instead, take the next scheduled dose at the usual time. Do not try to make up for the missed dose by taking a double dose.

What are possible side effects from using CHLORDIAZEPOXIDE?

These are not all the possible side effects you may have when taking CHLORDIAZEPOXIDE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- drowsiness,
- confusion,
- skin rash,
- swelling,
- menstrual irregularities,
- nausea and constipation,
- changes in sexual desire,
- falls and fractures

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Agranulocytosis (decrease in white blood cells): frequent infection with fever, chills, sore throat		√	
Amnesia (a type of memory loss): difficulty recalling events that recently happened.		√	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness, unexplained loss of appetite		√	
Mental and behavioural changes: aggression, rage, sudden anxiety or excitation, restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behavior		√	
Movement problems (ataxia and extrapyramidal symptoms): difficulty with fine motor tasks such as eating, writing or buttoning shirt; difficulty walking, loss of balance, slurring speech, trembling		√	
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure in the brain		√	
UNKNOWN			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			√
Respiratory Depression: slow, shallow or weak breathing.			√
Withdrawal		√	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Severe symptoms include: **Convulsions**: (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Catatonia**: feeling like you cannot move or respond **Delirium Tremens**: severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation**: feeling disconnected from reality **Hallucinations**: seeing or hearing things that are not there **Mania**: overactive behaviour and thoughts **Psychosis**: believing in things that are not true **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children. Store at room temperature (15°C – 30°C).

If you want more information about CHLORDIAZEPOXIDE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

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