PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

T/C**CHLORAX**

Chlordiazepoxide Hydrochloride, 5 mg

Clidinium Bromide, 2.5 mg

Capsule 5-2.5 mg, oral

USP

ATC Code: A03CA02

Anticholinergic-Anxiolytic

AA Pharma Inc.

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DEC 31, 1984

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.2 Geriatrics	12/2021
2 CONTRAINDICATIONS	12/2021
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	12/2021
4 DOSAGE AND ADMINISTRATION, 4.1 Dosing considerations	12/2021
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	12/2021
4 DOSAGE AND ADMINISTRATION, 4.4 Administration	12/2021
7 WARNINGS AND PRECAUTIONS	12/2021
7 WARNINGS AND PRECAUTIONS, 7.1.4 Geriatrics	12/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CHLORAX (chlordiazepoxide hydrochloride and clidinium bromide) is indicated for the following conditions when they are associated with excessive anxiety and tension:

- as adjunctive therapy in the treatment of peptic ulcer,
- in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and
- in the treatment of acute enterocolitis.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

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 4 DOSAGE AND ADMINISTRATION).

Long-term use of CHLORAX should be avoided in elderly patients. Enhanced monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS, Falls and fractures; DOSAGE AND ADMINISTRATION, 4.1 Dosing considerations).

2 CONTRAINDICATIONS

CHLORAX is contraindicated in the following conditions:

- cardiovascular instability
- history of drug abuse or dependence (chlodiazepoxide may predispose to habituation and dependence)
- impaired hepatic function (because of decreased metabolism)
- hiatal hernia with reflux esophagitis (clidinium may aggravate condition)
- intestinal atony of the elderly or debilitated (may result in obstruction due to clidinium's anticholinergic/antispasmodic effect)
- intestinal obstruction (may be exacerbated by clidinium)
- myasthenia gravis (clinidinium may aggravate condition because of inhibition of acetylcholine action)
- hypersensitivity to this drug 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);

- angle-closure, or predisposition to glaucoma;
- prostatic hypertrophy and benign bladder neck obstruction (anticholinergic effects may precipitate or aggravate urinary retention);
- Ulcerative colitis (clinidium may suppress intestinal motility and cause paralytic ileus; also, use may precipitate or aggravate the serious complications of toxic megacolon);
- psychotic disorders;
- Severe respiratory insufficiency

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including CHLORAX, 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 CHLORAX
- Monitor all patients regularly for the development of these behaviours or conditions.
- CHLORAX should be stored securely to avoid theft or misuse.

Withdrawal

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

- Avoid abrupt discontinuation or rapid dose reduction of CHLORAX.
- Terminate treatment with CHLORAX 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 CHLORAX 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

- Dosage should be individualized to each patient for maximum beneficial effects because of the varied individual responses to benzodiazepines and anticholinergics. The optimum dosage will vary with the diagnosis and response of the individual patient.
- Prolonged use of larger than usual therapeutic doses of chlordiazepoxide may result in psychic or physical dependence.
- CHLORAX should always be prescribed at the lowest effective dose for the shortest duration possible.
- CHLORAX 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 and/or Debilitated Patients

- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of CHLORAX should be avoided in geriatric patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adult (usual dose): The usual adult maintenance dose is 1 to 2 capsules 3 or 4 times/day, administered before meals and at bedtime.

Adult (prescribing limits): up to a total of 8 capsules daily (40 mg of chlordiazepoxide hydrochloride and 20 mg of clidinium bromide)

Pediatrics: Health Canada has not authorized an indication for pediatric use.

Geriatrics (>65 years of age): limit the dosage to the smallest effective amount to preclude the development of adverse reactions. No more than 2 capsules per day should be administered initially and increased gradually as needed and tolerated. Dosage should be limited to the smallest effective amount to preclude the development of ataxia, over sedation or confusion.

4.4 Administration

Administration of CHLORAX 30 to 60 minutes before meals is recommended to maximize absorption and, when used for reducing stomach acid formation, to allow its effect to coincide better with any antacid administration following the meal.

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Symptoms

Manifestations of chlordiazepoxide overdosage include somnolence, confusion, difficulty in urination, severe drowsiness, severe dryness of mouth, nose or throat, fast heart beat, unsual warmth, dryness, flushing of the skin, coma and diminished reflexes.

The symptoms of clidinium bromide overdosage progress from an intensification of the usual side effects (See 8 ADVERSE REACTIONS) to CNS disturbances ranging from restlessness and excitement to psychotic behavior, circulatory changes (flushing, tachycardia, fall in blood pressure), respiratory failure, paralysis and coma.

Treatment:

Employ general supportive measures, the recommended treatment of overdosage includes:

- emesis
- subcutaneous administration of 5 mg of pilocarpine, repeated as needed, until mouth is moist
- norepinephrine bitartrate or metaraminol infusions, to restore blood pressure
- caffeine and sodium benzoate, to treat CNS depression
- if excitation occurs, barbiturates should not be used since they may exacerbate excitation and/or prolong CNS depression
- Monitor respiration, pulse and blood pressure. Provide artificial respiration, if needed, for respiratory depression
- Administer i.v. fluids
- Dialysis is of limited value
- symptomatic treatment as necessary
- Administer physostigmine 0.5 to 2 mg at a rate of no more than 1 mg/minute. This may be repeated in 1 to 4 mg doses if arrhythmias, convulsions or deep coma recur.
- Administer i.v. fluids

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, 5 mg chlordiazepoxide hydrochloride and 2.5 mg clidinium bromide.	lactose monohydrate, microcrystalline cellulose, stearic acid, and talc. The capsule shell ingredients include: D&C yellow #10, FD&C green #3, gelatin, and titanium dioxide.

Each light green opaque body, light green opaque cap, hard gelatin capsule contains 5 mg chlordiazepoxide HCl and 2.5 mg clidinium bromide.

Bottles of 100, 500 and 1000.

7 WARNINGS AND PRECAUTIONS

General

Body temperature: In the presence of high environmental temperature, heat prostration may occur with the use of anticholinergics due to decreased sweating.

Concomitant use with opioids: Concomitant use of benzodiazepines, including CHLORAX, 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 use 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 CHLORAX 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 CHLORAX than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking CHLORAX, 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 CHLORAX is used with opioids.

Advise patients not to drive or operate heavy machinery with concomitant use of the opioid.

Cardiovascular

Hypertension may be aggravated by clidinium bromide. Risk-benefit should be considered when prescribing CHLORAX to patients with hypertension.

Dependence/Tolerance

Use of benzodiazepines, such as CHLORAX, 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 CHLORAX 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 CHLORAX. In individuals prone to substance use disorder, CHLORAX should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- CHLORAX 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 CHLORAX, 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, Withdrawal; 4.1 Dosing Considerations)

Driving and Operating Machinery

Patients receiving CHLORAX should be cautioned against engaging in hazardous activities requiring complete mental alertness, judgement and physical coordination, such as operating machinery or a motor vehicle.

Endocrine and Metabolism

Risk-benefit should be considered when prescribing CHLORAX to a patient with hyperthyroidism characterized by tachycardia, which may be increased by clidinium bromide.

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), geriatric or debilitated patients.

Gastrointestinal

Prolonged use of clinidium bromide may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort. Risk-benefit should be considered when prescribing CHLORAX to patients with xerostomia.

Immune

Severe Anaphylactic and Anaphylactoid Reactions: Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines, including LIBRAX. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with RESTORIL should not be rechallenged with the drug.

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

Complex sleep-related behaviours: Complex sleep-related behaviours such as "sleep- driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in patients who have taken CHLORAX. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with "sleep-driving", patients usually do not remember these events. The use of alcohol and other CNS-depressants with CHLORAX appears to increase the risk of such behaviours, as does the use of CHLORAX at doses exceeding the maximum recommended dose. CHLORAX is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of CHLORAX should be strongly considered for patients who report any such complex sleep-related behaviours.

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 geriatric patients may be at particular risk.

Ophthalmologic

Glaucoma: CHLORAX is contraindicated in patients with angle-closure, or predisposition to glaucoma (see 2 CONTRAINDICATIONS). Clinidium bromide's possible mydiatric effect may cause increase in intraocular pressure. This may precipitate an acute attack of angle-closure glaucoma.

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.

Mental and Emotional Disorders: Chlordiazepoxide hydrochloride may increase depression. Caution should be exercised if CHLORAX 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, rage, aggressive or hostile behaviour, anxiety, delusion, anger, increased muscle spasticity, sleep disturbances, nightmares, hallucinations and other adverse behavioural effects may occur due to chlordiazepoxide rare instances and in a random fashion. Should these occur, use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

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

Decreased excretion may increase risk of side effects in patients with renal function impairment. CHLORAX should be administered with caution to patients with a history of renal disease.

Reproduction Health: Female and Male Potential

Teratogenic Risk: The use of CHLORAX in pregnancy is generally not recommended

Chlordiazepoxide hydrochloride: Chlordiazepoixde HCl crosses the placenta. It has been reported to increase the risk of congenital malformations when used during the first trimester of pregnancy.
Clidinium bromide: appropriate studies in humans have not been performed. However, reproduction studies in rats havenot shown that clidinium has adverse effects on the foetus.

Non-teratogenic Risk:

Chlordiazepoxide hydrochloride: Chronic use of chlordiazepoxide during pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. Use of chlordiazepoxide just prior to or during labour may cause neonatal flaccidity.

Clidinium bromide: appropriate studies in humans have not been performed. However, reproduction studies in rats havenot shown that clidinium has adverse effects on the foetus.

Respiratory

Severe Chronic Obstructive Pulmonary Disease: Anticholinergic effects may cause thickening of secretions and impair expectorations; ventilatory failure may be exacerbated with the use of chlordiazepoxide hydrochloride. Risk-benefit should be considered when prescribing CHLORAX to patients with severe chronic obstructive pulmonary disease.

Sensitivity/Resistance

Patients who are sensitive to other benzodiazepines or any of the belladonna alkaloids may be sensitive to CHLORAX as well.

7.1 Special Populations

7.1.1 Pregnant Women

The use of CHLORAX (anticholinergic and anxiolytic combination) in pregnancy is not recommended.

Chlordiazepoxide: Chlordiazepoxide hydrochloride crosses the placenta. It has been reported to increase the risk of congenital malformations when used during the first trimester of pregnancy. Chronic use of chlordiazepoxide during pregnancy may cause physical dependence with resulting withdrawal symptoms in the neonate. Use of chlordiazepoxide just prior to or during labour may cause neonatal flaccidity.

Clidinium: appropriate studies in humans have not been performed. However, reproduction studies in rats havenot shown that clidinium has adverse effects on the foetus.

Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided

7.1.2 Breast-feeding

Chlordiazepoxide hydrochloride or its metabolites may be excreted in breast milk; use by nursing mothers maycause sedation in the infant.
Clidinium may tend to inhibit lactation.

CHLORAX should not be administered to breast-feeding women, unless the expected benefit to the mother outweighs the potential risk to the infant.

7.1.3 Pediatrics

Pediatrics(<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

No information is available on the relationship of age to the effect of chlordiazepoxide and clidinium in paediatric patients. However, it is known that infants and young children are especially susceptible to the toxic effects of atropine-like drugs, such as clidinium, and to the central nervous system effects of benzodiazepines, such as chlordiazepoxide.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): In the elderly, limit the dosage to the smallest effective amount to preclude the development of adverse reactions. (see 4 DOSAGE AND ADMINISTRATION).

Long-term use of CHLORAX 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.

Geriatric patients may respond to usual doses of chlordiazepoxide and clidinium with excitement,agitation, drowsiness, or confusion.

Geriatric patients are especially susceptible to the anticholinergic side effects, such as constipation,dryness of mouth, and urinary retention (especially in males), of clidinium. If these side-effects occur and continue or are severe, medication should be discontinued.

Caution is also recommended when clidinium is given to geriatric patients, because of the danger of precipitating undiagnosed glaucoma.

Memory may become severely impaired in geriatric patients, especially those who already have memory problems, with the continued use of clidinium since this medication blocks the action of acetylcholine, which is responsible for many functions of the brain, including memory function.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following adverse reactions have been reported with the use of CHLORAX:

- **Blood and Lymphatic System Disorders:** agranulocytosis; granulocytopenia, leukopenia
- **Eye Disorders:** increased intraocular pressure (eye pain), blurred vision
- **Gastrointestinal disorders:** decreased peristalsis - possible paralytic ileus (constipation), bloated feeling, dryness of mouth, nausea, stomach cramps. Constipation may occur when chlordiazepoxide plus clidinium therapy is combined with other spasmolytics and/or a low residue diet.
- **General Disorders and Administration Site Conditions:** edema, unusual tiredness or weakness
- **Hepatobiliary Disorders:** hepatic dysfunction, jaundice
- **Musculoskeletal and Connective Tissue Disorders:** muscle cramps
- **Nervous System Disorders:** CNS depression (slow heartbeat, shortness of breath, or troubled breathing), dizziness, drowsiness, confusion, ataxia, headache, trembling, seizures, extrapyramidal symptoms; changes in EEG patterns (low-voltage fast activity) have been observed in patients during and after chlordiazepoxide hydrochloride treatment
- **Psychiatric Disorders:** paradoxical reactions (trouble in sleeping, unusual excitement, nervousness or irritability), decreased sexual ability
- **Renal and urinary disorders:** urinary hesitancy
- **Reproductive System and Breast Disorders:** increased and decreased in libido, minor menstrual irregularities
- **Skin and Subcutaneous Tissue Disorders:** skin eruptions, skin rash or hives, decreased sweating

From the adverse reactions listed above, skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, as well as increased and decreased libido have been infrequent and are generally controlled with reduction of dosage.

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 CHLORAX. 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 CHLORAX 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, Risks from Concomitant use with Opioids)

9.2 Drug interactions overview

Benzodiazepines, including CHLORAX, may produce additive CNS depressant effects when co-administered with alcohol, and medications, including opioids, which themselves can produce CNS depression.

The activity of benzodiazepines, including CHLORAX, may be enhanced by compounds which inhibit certain hepatic enzymes such as cytochrome P450 3A enzymes.

9.3 Drug-behavioural interactions

Benzodiazepines, including CHLORAX, may produce additive CNS depressant effects when co-administered with alcohol. Patients should be cautioned not to take alcohol because of the potentiation of effect that might occur.

9.4 Drug-drug interactions

CNS depressant drugs: Benzodiazepines, including CHLORAX, may produce additive CNS depressant effects when co-administered sedative antihistamines, narcotic analgesics, anticonvulsants, antipsychotics (neuroleptics), anesthetics, antidepressant agents or psychotropic medications which themselves can produce CNS depression.

Cytochrome P450: Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 3A) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Examples include cimetidine,-erythromycin, ketoconazole, itroconazole, nefazodone and several HIV protease inhibitors.

Opioids: Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including CHLORAX, 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).

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 hydrochloride is a benzodiazepine CNS depressant with anxiolytic and sedative properties.

Although the mechanism of action for the behavioral and neurophysiological effects of benzodiazepines has not been defined, it is postulated that they exert their antianxiety effect by selective inhibition of electrical discharge from the limbic system without depression of the rest of the brain or autonomic nervous system.

Clidinium bromide is a synthetic quaternary ammonium agent with anticholinergic and antispasmodic activity. It inhibits gastrointestinal motility and diminishes gastric acid secretion. The drug's anticholinergic activity approximates that of atropine sulfate and propantheline bromide.

10.2 Pharmacodynamics

Information is not available.

10.3 Pharmacokinetics

Information is not available.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C) in a tightly closed, light resistant container.

Keep out of reach and sight of children.

CHLORAX 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:	(1) 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-,4-oxide, monohydro-chloride; (2) 7-Chloro-2-(methylamino)-5-phenyl-3-H-1,4-benzodiazepine 4-oxide monohydro-chloride;
Molecular formula and molecular mass:	$C_{16}H_{14}ClN_3O.HCl$ and 336.22 g/mol
Structural formula:	Information is not available.
Physicochemical properties:	Information is not available.

Proper name:	clidinium bromide
Chemical name:	(1) 1-Azoniabicyclo [2.2.2] octane, 3-[(hydroxy-diphenylacetyl)oxy]-1-methyl; bromide; (2) 3-Hydroxy-1-methylquinuclidinium bromide benzilate
Molecular formula and molecular mass:	$C_{22}H_{26}BrNO_3$ and 432.36 g/mol
Structural formula:	Information is not available.
Physicochemical properties:	Information is not available.

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 CHLORAX affects fertility in males or females.

Special Toxicology: Information is not available.

Juvenile Toxicity: Information is not available.

17 SUPPORTING PRODUCT MONOGRAPHS

1. LIBRAX (Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules, 5mg / 2.5mg), submission control 227411, Prescribing Information, Bausch Health, Canada Inc. (JUN 11, 2019)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

T/C**CHLORAX**

Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules

Read this carefully before you start taking **CHLORAX** 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 **CHLORAX**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take CHLORAX 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 CHLORAX with:

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

Your healthcare professional should:

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

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

Withdrawal: If you suddenly stop taking CHLORAX, 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 CHLORAX or changing your medicine.**

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

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

What is CHLORAX used for?

CHLORAX is used to treat the following conditions when they are associated with anxiety and tension:

- Peptic ulcers (open sores in the lining of your stomach and small intestine)
- Irritable bowel syndrome (irritable colon, spastic colon, mucous colitis)
- Acute entero-colitis (inflammation of the colon)

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

How does CHLORAX work?

CHLORAX belongs to a group of medications called benzodiazepines. It affects chemical activity in your brain to help promote sleep and to reduce anxiety and worry. It also works by slowing down the natural movements of your stomach and lower intestine to relieve stomach pain or discomfort. This helps to treat peptic ulcers, irritable bowel syndrome and acute entero-colitis.

What are the ingredients in CHLORAX?

Medicinal ingredients: chlordiazepoxide hydrochloride and clidinium bromide.

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

The capsule shell ingredients include: D&C yellow #10, FD&C green #3, gelatin and titanium dioxide.

CHLORAX comes in the following dosage forms:

Capsule: 5 mg chlordiazepoxide hydrochloride and 2.5 mg clidinium bromide.

Do not use CHLORAX if:

- you have any heart instability;
- you have a history of drug abuse or dependence;
- you have any liver problems;
- you have a hiatal hernia (a condition where the top of your stomach bulges through an opening in your diaphragm) with acid reflux;
- you are elderly or very weak and have intestinal or bowel problems;
- you have an intestinal obstruction;
- you have myasthenia gravis (a disease that causes weakness in your muscles);
- you have an enlarged prostate gland or are unable to voluntarily urinate (urinary retention);
- you have ulcerative colitis (an inflammatory bowel disease);
- you are allergic to chlordiazepoxide hydrochloride or clidinium bromide or any of the non-medicinal ingredients in CHLORAX (see **What are the ingredients in CHLORAX?**);
- you have angle-closure glaucoma or are at risk of developing glaucoma (eye disorder);
- you have mental health disorder (psychosis).
- You have severe lung or breathing problems

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

- have open-angle glaucoma
- have high blood pressure
- have an overactive thyroid (hyperthyroidism)
- have depression or psychosis
- have a type of lung disease called chronic obstructive pulmonary disease (COPD)
- have any kidney problems
- have memory problems
- have impaired thinking, confusion or any other type of brain damage
- have dry mouth
- are allergic to any other benzodiazepines or anticholinergic medications
- are taking pain killers, known as opioids
- 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)
- live or work in a high temperature environment
- are sensitive to drugs known as benzodiazepines, atropine or belladonna
- are 65 years of age or older
- are pregnant, think you may be pregnant or are planning to become pregnant, CHLORAX may harm your baby
- are breastfeeding, CHLORAX may harm your baby
- have lactose intolerance.

Other warnings you should know about:

Pregnancy and Breastfeeding: Benzodiazepines such as CHLORAX may harm your unborn baby (e.g. birth defects) if you take them while you are pregnant. The risk is higher if you take CHLORAX during the first trimester of pregnancy, just before labour, or during labour. If you are able to get pregnant, want to be pregnant, or think you are pregnant, there are specific risks you should discuss with your healthcare professional. CHLORAX may stop lactation and/or cause unwanted side effects to your baby if you take it while breastfeeding.

Driving and using machines: CHLORAX may affect your ability to be alert. This may be made worse if you drink alcohol or take other sedatives. Do not drive or use machinery while you are taking CHLORAX until you know how it affects you. Avoid driving or using machinery if taking CHLORAX with other sedatives.

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 CHLORAX.

Your risk of going through withdrawal is higher if you are taking CHLORAX for a long time or at high doses. However, symptoms can still occur if you are taking CHLORAX 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 CHLORAX 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

CHLORAX with Opioids: Taking CHLORAX 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 CHLORAX

Do NOT drive or operate heavy machinery or do tasks that require special attention if you are taking an opioid medicine and CHLORAX.

Falls and Fractures: Benzodiazepines like CHLORAX 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

Dental Problems: If you use CHLORAX for a long time, it may cause you to produce less saliva or it might stop your saliva production. This may cause dental problems such as cavities, swollen gums or gingivitis, oral thrush and/or discomfort.

Monitoring and Tests: During your treatment with CHLORAX, your healthcare professional may do tests including tests to monitor your blood cell count and your liver function.

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

Serious Drug Interactions

Taking CHLORAX and opioids may cause:

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

The following may also interact with CHLORAX:

- Alcohol
- Sedative antihistamines
- Medications used to treat epilepsy (anticonvulsants)
- Medications used to manage psychosis (antipsychotics)
- Medications used to treat depression (antidepressants)
- Medications that affect your mind, emotions, or behaviour (psychotropics)
- Cimetidine, a medicine used to treat heartburn and stomach ulcers
- Erythromycin, a medicine used to treat bacterial infections
- Ketoconazole or itraconazole, which are medicines used to treat fungal infections
- Nefazodone, a medicine used to treat depression
- Certain medicines used to treat HIV/AIDS

How to take CHLORAX:

- Take CHLORAX exactly as your healthcare professional tells you to take it.
- Take CHLORAX before meals and at bedtime.
- Swallow the capsules with some water.

Usual dose:

Adults (18 to 64 years of age): 1 to 2 capsules 3 or 4 times per day before meals and at bedtime. The maximum dose is 8 capsules per day.

Elderly (65 years of age and older): The starting dose is 1 capsule 2 times per day.

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:

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

Missed Dose:

If you forget to take CHLORAX capsules at the correct time, take it as soon as you remember. If it is almost time for the next dose, skip the missed dose and continue to take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using CHLORAX?

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

- Headache
- Dizziness
- Drowsiness
- Unusual tiredness or weakness
- Blurred vision
- Dry mouth
- Feeling bloated
- Stomach or muscle cramps
- Constipation
- Nausea
- Skin rash or hives
- Decreased sweating
- Decreased sexual ability; changes in sexual desire
- Menstrual irregularities
- Falls and fractures.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	

LESS COMMON			
Confusion, memory loss		✓	
RARE			
Agranulocytosis (severe reduction in white blood cell count): fever, chills, low blood pressure			✓
Depression: Depressed mood; thoughts of death or suicide		✓	
Mental and behavioural changes: Unexpected reactions such as agitation, anxiety, hyperactivity, excitement, hallucination, impaired concentration or memory, worsened insomnia, feeling nervous, irritable, increased muscle spasticity, aggressiveness, irritability, rages, psychoses and violent behavior		✓	
Movement problems: ataxia (including unsteadiness and clumsiness), difficulty controlling movements, trembling (extrapyramidal symptoms)		✓	
Severe allergic reaction: skin reactions (rash, hives), swelling including of the tongue or throat, trouble breathing, nausea and vomiting			✓
Syncope(fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		✓	
UNKNOWN FREQUENCY			
Blurred vision, eye pain		✓	
Hepatic dysfunction (liver function abnormalities)**:** jaundice (yellowing of the skin and eyes), dark urine, light coloured stool, itching all over your body			✓
Oedema: swelling of hands, ankles or feet.		✓	
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.			
Seizures (fits): uncontrollable shaking with or without loss of consciousness		✓	
Somnambulism (sleep-walking): getting out of bed while not fully awake, including preparing and eating food, making phone calls, leaving the house, etc.		✓	
Urinary hesitancy: trouble starting or maintaining urine flow		✓	
Withdrawal: **Severe symptoms include:** **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 **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **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:

Store at room temperature (15-30°C) in a tightly closed, light resistant container. Keep out of reach and sight of children.

If you want more information about CHLORAX:

- 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, Vaughan, Ontario, L4K 4N7.

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