PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

T/C**LIBRAX®**

Chlordiazepoxide Hydrochloride, 5 mg

Clidinium Bromide, 2.5 mg

Capsules, Oral

USP

Anxiolytic-Anticholinergic Agent

Bausch Health, Canada Inc
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

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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
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LIBRAX (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)
- in the treatment of acute enterocolitis

1.1 Pediatrics

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

Long-term use of LIBRAX should be avoided in geriatric patients. Enhanced monitoring is recommended (see 4.1 Dosing considerations; 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).

2 CONTRAINDICATIONS

LIBRAX is contraindicated in patients with:

- hypersensitivity to chlordiazepoxide, clidinium 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.
- cardiovascular instability
- a history of drug abuse or dependence (chlordiazepoxide may predispose to habituation and dependence)
- angle-closure, or predisposition to glaucoma (clidinium has a possible mydriatic effect resulting in increased intraocular pressure may precipitate an acute attack of angle-closure glaucoma)
- 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 (clidinium may aggravate condition because of inhibition of acetylcholine action)
- prostatic hypertrophy or urinary retention (anticholinergic effects may precipitate or aggravate urinary retention)
- ulcerative colitis (clidinium may suppress intestinal motility and cause paralytic ileus; also, use may precipitate or aggravate the serious complications of toxic megacolon)
- severe respiratory insufficiency

- psychotic disorders

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

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

Withdrawal

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

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

- LIBRAX should always be prescribed at the lowest effective dose for the shortest duration possible.
- Dosage should be individualized to each patient.
- Prolonged use of larger than usual therapeutic doses of chlordiazepoxide may result in psychic or physical dependence.

Discontinuation

- LIBRAX 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 and debilitated patients may respond to the usual doses with excitement, agitation, drowsiness, or confusion; lower doses may be required for such patients.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of LIBRAX should be avoided in geriatric patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adults: 1 or 2 capsules, one to four times a day, thirty to sixty minutes before meals or food, the dosage then being adjusted as needed and tolerated.

Prescribing limit: up to a total of 8 capsules daily (40 mg of chlordiazepoxide hydrochloride and 20 mg of clidinium bromide)

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

Geriatrics (>65 years of age): Initially no more than 1 capsule two times a day, the dosage then being adjusted as needed and tolerated. Dosage should be limited to the smallest effective amount to preclude the development of ataxia, oversedation or confusion.

4.4 Administration

Administration of LIBRAX® 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

Confusion; difficulty in urination; severe drowsiness; severe dryness of mouth, nose, or throat; fast

heartbeat; unusual warmth, dryness, and flushing of the skin.

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 and provide artificial respiration, if needed, for respiratory depression
- administer i.v. fluids
- symptomatic treatment as necessary
- dialysis is of limited value

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Capsule chlordiazepoxide hydrochloride, 5mg clidinium bromide, 2.5mg	Gelatin, lactose monohydrate, starch, talc, titanium dioxide, D&C Yellow # 10, FD&C Green, black imprinting ink.

Each green #4 capsule imprinted with LIBRAX contains 5 mg chlordiazepoxide hydrochloride and 2.5 mg clidinium bromide. Available in bottles of 100 capsules.

7 WARNING AND PRECAUTIONS

General

Body Temperature: When clidinium is given to patients where the environmental temperature is high, there is risk of a rapid increase in body temperature because of suppression of sweat gland activity.

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

Cardiovascular

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

Dependence/Tolerance

Use of benzodiazepines, such as LIBRAX, 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 LIBRAX 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 LIBRAX. In individuals prone to substance use disorder, LIBRAX should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- LIBRAX 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 LIBRAX, 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 LIBRAX 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 LIBRAX 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 clidinium 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 LIBRAX 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 LIBRAX. 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 LIBRAX appears to increase the risk of such behaviours, as does the use of LIBRAX at doses exceeding the maximum recommended dose. LIBRAX 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 LIBRAX 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: LIBRAX is contraindicated in patients with angle-closure, or predisposition to glaucoma (see 2 CONTRAINDICATIONS). Clidinium bromide's possible mydriatic 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 LIBRAX 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. LIBRAX should be administered with caution to patients with a history of renal disease.

Reproductive Health: Female and Male Potential

- **Teratogenic Risk**

There are no adequate and well-controlled studies of LIBRAX in pregnant women. Animal studies with other anxiolytic-sedative agents have suggested increased risk of congenital malformations (see 7.1.1 Pregnant women; 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

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. (see 7.1.1 Pregnant Women)

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 LIBRAX 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 LIBRAX as well.

7.1 Special Populations

7.1.1 Pregnant Women

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

Chlordiazepoxide: Chlordiazepoxide crosses the placenta. 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. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided.

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.

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

7.1.2 Breast-feeding

Chlordiazepoxide or its metabolites may be excreted in breast milk; use by breast-feeding mothers may cause sedation in the infant.

Clidinium may inhibit lactation.

LIBRAX 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): 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 pediatric 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): Dosage should be limited to the smallest effective amount to preclude the development of ataxia, oversedation or confusion.

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.

Long-term use of LIBRAX should be avoided in geriatric 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. (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures)

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

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 has occurred more often when LIBRAX therapy has been combined with other spasmolytic agents 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; syncope; extrapyramidal symptoms; changes in EEG patterns (low-voltage fast activity) have been observed in patients during and after chlordiazepoxide hydrochloride treatment

Psychiatric Disorders: paradoxical reaction (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 libido; minor menstrual irregularities

Skin and Subcutaneous Tissue Disorders: 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 LIBRAX. 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 LIBRAX 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 LIBRAX, 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 LIBRAX, may be enhanced by compounds which inhibit certain hepatic enzymes such as cytochrome P450 enzymes.

9.3 Drug-Behavioural Interactions

Benzodiazepines, including LIBRAX, 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 LIBRAX, 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) 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 LIBRAX, 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
Benzodiazepines, such as chlordiazepoxide hydrochloride, act as depressants of the central nervous system, producing all levels of CNS depression from mild sedation to hypnosis to coma depending on the dose taken.

Clidinium bromide
Anticholinergics, such as clidinium bromide, inhibit the muscarinic actions of acetylcholine on structures innervated by postganglionic cholinergic nerves as well as on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These postganglionic receptor sites are present in the autonomic effector cells of the smooth muscle, cardiac muscle, sinoatrial and atrioventricular nodes, and exocrine glands. Depending on the dose, anticholinergics may reduce the motility and secretory activity of the gastrointestinal system. (see 7 WARNINGS AND PRECAUTIONS, Gastrointestinal)

10.2 Pharmacodynamics

Chlordiazepoxide hydrochloride
Pharmacologic experiments have shown that chlordiazepoxide hydrochloride is a potent central nervous system depressant and muscle relaxant.

The dose which induces definite neurologic symptoms in various animal species is in the range of 10-40 mg/kg p.o.; effects on behaviour and aggression can be seen with administration of 1-3 mg/kg, p.o., in more sensitive tests. Hostile monkeys were made tame by oral doses which did not cause sedation but eliminated fear and aggression. The taming effect was further demonstrated in rats made vicious by lesions in the septal area in the brain.

Clidinium bromide
Clidinium bromide is a quaternary ammonium compound with anticholinergic and antispasmodic activity. Clidinium bromide inhibits gastrointestinal motility and gastric secretions. As an anticholinergic agent, its activity approximates that of atropine sulfate against acetylcholine-induced spasms in isolated intestinal strips. In mice, oral administration proved it to be an effective antisialagogue in preventing pilocarpine-induced salivation. Spontaneous intestinal motility in both rats and dogs is reduced following oral dosing with 0.1 to 0.25 mg/kg.

Potent cholinergic ganglionic blocking effects (vagal) are produced with intravenous usage in anaesthetized dogs. Oral doses of 2.5 mg/kg to dogs produced signs of nasal dryness and slight pupillary dilation. In monkeys and rabbits, doses of 5 mg/kg p.o., given 3 times daily for 5 days did not produce apparent secretory or visual changes.

10.3 Pharmacokinetics

Absorption

Chlordiazepoxide hydrochloride is well absorbed from the gastrointestinal tract within 1 to 2 hours. Metabolic studies in animals and man have indicated that oral chlordiazepoxide hydrochloride is rapidly absorbed from the gastro-intestinal tract.

Clidinium bromide is poorly and very irregularly absorbed from the gastrointestinal tract. The action of clidinium bromide starts at about 1 hour after ingestion and lasts for approximately 3 hours.

Distribution
Chlordiazepoxide hydrochloride is highly protein bound (96%).

Metabolism
Chlordiazepoxide hydrochloride and clidinium bromide are both metabolized in the liver. Chlordiazepoxide hydrochloride is demethylated to a metabolite identified as Ro 5-0883, deaminated to the "lactam" Ro 5-2092 and finally converted to the "open lactam" which is pharmacologically inert and is excreted in the urine as such or in the form of alkali-labile conjugates. Repeated administration of 20 mg of chlordiazepoxide b.i.d. for 14 days to adult subjects produced serum levels of about 2 µg/mL of chlordiazepoxide, 1 µg/mL of the demethylated metabolite Ro 5-0883, and 1 µg/mL of the "lactam" Ro 5-2092.

Elimination
The biological half-life for chlordiazepoxide hydrochloride is between 5 and 30 hours. In man, the half-life of chlordiazepoxide hydrochloride in plasma is 22-24 hours; in dogs 10-14 hours. Chlordiazepoxide hydrochloride is eliminated by the kidneys and clidinium bromide by the kidneys and in the feces.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C)

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Chlordiazepoxide hydrochloride

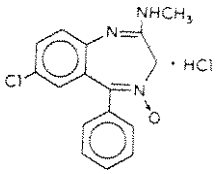
Proper name: chlordiazepoxide hydrochloride

Chemical name: (1) 3H-1,4-Benzodiazepin-2-amine, 7-chloro-N-methyl-5-phenyl-, 4-oxide, monohydrochloride

(2) 7-Chloro-2-(methylamino)-5-phenyl-3-H-1,4-benzodiazepine 4-oxide monohydrochloride

Molecular formula and molecular mass: $C_{16}H_{14}ClN_30.HCl$ and 336.22g/mol

Structural formula:



Clidinium bromide

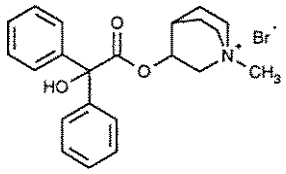
Proper name: clidinium bromide

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: $C_{22}H_{26}BrN0_3$ and 432.36 g/mol

Structural formula:



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

Chlordiazepoxide hydrochloride
The oral LD_{50} of single doses of chlordiazepoxide hydrochloride is 720±51 mg/kg, as determined in mice observed for a period of five days following dosage.

Chronic toxicity studies in rats, dogs, monkeys and chicken have shown that chlordiazepoxide hydrochloride did not exhibit specific organotoxic properties.

Clidinium bromide
The oral LD_{50} of single doses of clidinium bromide is 860±57 mg/kg as determined in mice observed for a period of 5 days following dosage.

Reproductive and Developmental Toxicology

Chlordiazepoxide hydrochloride
In rats, reproduction studies in which chlordiazepoxide hydrochloride was administered orally at doses of 10, 20, and 80 mg/kg/day showed no congenital anomalies, no effect on lactation or growth of the off-spring.

However, at an oral dose of 100 mg/kg/day, there was observed a significant decrease in the fertilization rate and a marked decrease in the viability and body weight of the offspring which may be attributed to sedation of dams.

Clidinium bromide
Studies in rats employing dosages of 2.5 and 10 mg/kg/day of clidinium bromide showed no significant effects on fertility, gestation, viability of off-spring, lactation, or fetal abnormalities.

Chlordiazepoxide hydrochloride and Clidinium bromide combination
In a rat reproductive study, oral daily doses were administered through two successive matings, in two concentrations of 2.5 mg/kg chlordiazepoxide hydrochloride with 1.25 mg/kg clidinium bromide, or 25 mg/kg chlordiazepoxide hydrochloride with 12.5 mg/kg clidinium bromide. No significant differences were noted between the control and treated groups, except a slight decrease in the number of animals surviving through lactation at the highest dosage in the first mating, and a slight decrease in the number of pregnant females and in the percentage of off-spring surviving until weaning in the second mating.

PATIENT MEDICAL INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

T/CLIBRAX
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules

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

Serious Warnings and Precautions

<u>Addiction, Abuse and Misuse:</u> Even if you take LIBRAX 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 LIBRAX with:

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

Your healthcare professional should:

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

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

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

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

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

What is LIBRAX used for?
LIBRAX 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 LIBRAX. LIBRAX may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does LIBRAX work?
LIBRAX 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 enterocolitis.

What are the ingredients in LIBRAX ?
Medicinal ingredients: chlordiazepoxide hydrochloride and clidinium bromide.
Non-medicinal ingredients: Gelatin, lactose monohydrate, starch, talc, titanium dioxide, D&C Yellow # 10, FD&C Green, black imprinting ink.

LIBRAX comes in the following dosage forms:
Capsule: 5 mg chlordiazepoxide hydrochloride and 2.5 mg clidinium bromide.

Do not use LIBRAX if:

- you have any heart instability
- you have a history of drug abuse or dependence
- you have angle-closure glaucoma (eye disorder), or are at risk of developing glaucoma
- 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 and/or clidinium bromide, or to any of the ingredients in LIBRAX (see **What are the ingredients in LIBRAX?**)
- you have severe lung or breathing problems
- you have a mental health disorder (psychosis)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIBRAX. 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, LIBRAX may harm your baby
- are breastfeeding, LIBRAX may harm your baby

Other warnings you should know about:

Pregnancy and Breastfeeding: Benzodiazepines such as LIBRAX may harm your unborn baby (e.g. birth defects) if you take them while you are pregnant. The risk is higher if you take LIBRAX 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. LIBRAX may stop lactation and/or cause unwanted side effects to your baby if you take it while breastfeeding.

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 LIBRAX.

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

LIBRAX with Opioids: Taking LIBRAX 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 LIBRAX

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

Falls and Fractures: Benzodiazepines like LIBRAX 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 LIBRAX 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 LIBRAX, your healthcare professional may do 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 LIBRAX and opioids may cause: • **severe drowsiness** • **trouble breathing** • **coma death** • **death**

The following may also interact with LIBRAX:

- 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 LIBRAX:

- Take LIBRAX exactly as your healthcare professional tells you to take it
- Take LIBRAX before meals

Usual dose:

Adults (18 to 64 years of age): 1 or 2 capsules one to four times a day, 30 to 60 minutes before meals or food. The maximum dose is 8 capsules per day.

Elderly (65 years of age and older): The starting dose is no more than 1 capsule two times a day.

Your doctor will slowly decrease your dose and will tell you when to stop taking this medication. 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 LIBRAX, 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 LIBRAX 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 LIBRAX?

These are not all the possible side effects you may have when taking LIBRAX. 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), trembling (extrapyramidal symptoms)		✓	
Severe allergic reaction: skin reactions (skin eruptions, 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 of 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 (sleepwalking): getting out of bed while not fully awake and do activities you do not remember the day after, or sleep driving		✓	
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°C to 30°C)

Keep out of reach and sight of children.

If you want more information about LIBRAX:

- 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, or by calling 1-800-361-4261.

This leaflet was prepared by Bausch Health, Canada Inc.

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