PRESCRIBING INFORMATION

LIBRAX®

(Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules, USP)

Anxiolytic-Anticholinergic Agent

Valeant Canada LP
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

Date of Preparation:
September 21, 2004

Address Updated:
September 04, 2014

Control#: 094065

PRESCRIBING INFORMATION

LIBRAX®

(Chlordiazepoxide Hydrochloride, USP and
Clidinium Bromide, USP)

Anxiolytic-Anticholinergic Agent

ACTION AND CLINICAL PHARMACOLOGY

Chlordiazepoxide: Benzodiazepines, such as chlordiazepoxide, 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: Anticholinergics, such as clidinium, 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.

Absorption: Chlordiazepoxide is well absorbed from the gastrointestinal tract within 1 to 2 hours.
Clidinium is poorly and very irregularly absorbed from the gastrointestinal tract.

Protein binding: chlordiazepoxide is highly protein bound (96 %).

Biotransformation: chlordiazepoxide and clidinium are both metabolized in the liver.

Half-life: the biological half-life for chlordiazepoxide is between 5 and 30 hours.

Onset of action: the action of clidinium starts at about 1 hour after ingestion and lasts for approximately 3 hours.

Elimination: Chlordiazepoxide is eliminated by the kidneys and clidinium by the kidneys and in the feces.

INDICATIONS AND CLINICAL USE

Librax® (chlordiazepoxide hydrochloride and clidinium bromide) is indicated as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute entero-colitis, when these are associated with excessive anxiety and tension.

CONTRAINDICATIONS

Librax® (chlordiazepoxide hydrochloride and clidinium bromide) is contraindicated in the following conditions:

- cardiovascular instability
- 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)
- sensitivity to chlordiazepoxide and/or clidinium

WARNINGS

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.

Risk-benefit should be considered when the following medical problems exist:

- open-angle glaucoma (clidinium's possible mydriatic effect may cause a slight increase in intraocular pressure; glaucoma therapy may need to be adjusted)

- hypertension (may be aggravated by clidinium)

- hyperthyroidism (characterized by tachycardia, which may be increased by clidinium)

- mental depression (chlordiazepoxide may increase depression)

- psychoses (paradoxical reactions may occur due to chlordiazepoxide)

- 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)

- renal function impairment (decreased excretion may increase risk of side effects)

- xerostomia (prolonged use of clidinium may further reduce limited salivary flow)

PRECAUTIONS

Caution is recommended in debilitated patients since they may show an increased susceptibility to this medication.

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

Pregnancy/Reproduction

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

Chlordiazepoxide: Chlordiazepoxide 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 labor 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 fetus.

Breast-feeding

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

Pediatrics

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.

Geriatrics

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.

Dental

Prolonged use of clidinium may decrease or inhibit salivary flow, thus contributing to the development of caries, periodontal disease, oral candidiasis, and discomfort.

ADVERSE REACTIONS

The following adverse reactions have been reported with the use of LIBRAX® (chlordiazepoxide hydrochloride and clidinium bromide):

- hematopoietic: agranulocytosis; granulocytopenia; leukopenia

- CNS: depression (slow heartbeat, shortness of breath, or troubled breathing)

- GI tract: decreased peristalsis - possible paralytic ileus (constipation)

- Others: skin rash or hives; increased intraocular pressure (eye pain); jaundice; paradoxical reaction (trouble in sleeping; unusual excitement; nervousness, or irritability); bloated feeling; decreased sweating; dizziness; drowsiness; dryness of mouth; headache; blurred vision; decreased sexual ability; nausea; unusual tiredness or weakness; muscle cramps; stomach cramps; trembling; seizures.

SYMPTOMS AND TREATMENT OF 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: the recommended treatment of overdosage includes:

- emesis or gastric lavage with 4 % tannic acid solution
- 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
- artificial respiration, if needed, for respiratory depression
- symptomatic treatment as necessary

DOSAGE AND ADMINISTRATION

General Dosing Information:

- dosage should be adjusted to meet the individual requirements of each patient since response varies according to the severity of the condition.
- geriatric and debilitated patients may respond to the usual doses with excitement, agitation, drowsiness, or confusion; lower doses may be required for such patients.

- 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.

- prolonged use of larger than usual therapeutic doses of chlordiazepoxide may result in psychic or physical dependence.

- following prolonged administration, chlordiazepoxide should be withdrawn gradually in order to avoid the possibility of precipitating withdrawal symptoms.

Usual Oral Dose (Adult): 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.

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

Usual Oral Dose (Pediatrics): Dosage has not been established

Usual Oral Dose (Geriatrics): Initially no more than 1 capsule two times a day, the dosage then being adjusted as needed and tolerated.

PHARMACEUTICAL INFORMATION

Drug Substances:

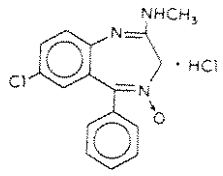
1. **Chlordiazepoxide Hydrochloride**, USP

(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;

Empirical formula: $C_{16}H_{14}ClN_30.HCl$

Structural formula:



Molecular weight: 336.22

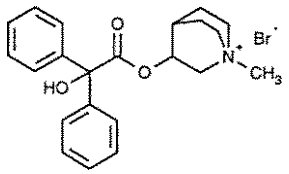
2. **Clidinium Bromide**, USP

(1) 1-Azoniabicyclo[2.2.2]octane, 3-[(hydroxydiphenylacetyl)oxy]-1-methyl;, bromide;

(2) 3-Hydroxy-1-methylquinuclidinium bromide benzilate

Empirical formula: $C_{22}H_{26}BrN0_3$

Structural formula:



Molecular Weight: 432.36

COMPOSITION

Each LIBRAX® (chlordiazepoxide hydrochloride and clidinium bromide) capsule contains:

- chlordiazepoxide hydrochloride, USP
- clidinium bromide, USP
- lactose
- starch

STORAGE RECOMMENDATIONS

LIBRAX® capsules should be stored in a well-closed container at controlled room temperature (15-30^{o} C).

AVAILABILITY

Each green # 4 capsule, imprinted with LIBRAX in black ink on body and cap, contains Chlordiazepoxide hydrochloride, USP 5 mg and clidinium bromide, USP 2.5 mg. Available in bottles of 100 and 500 capsules.

PHARMACOLOGY

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.

Metabolic studies in animals and man have indicated that oral chlordiazepoxide hydrochloride is rapidly absorbed from the gastro-intestinal tract. Chlordiazepoxide 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. In man, the half-life of chlordiazepoxide hydrochloride in plasma is 22-24 hours; in dogs 10-14 hours.

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.

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.

REPRODUCTION AND TERATOLOGY

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.

REFERENCES

1. Browne T.R. and Penry J.K. Benzodiazepines in the Treatment of Epilepsy. A Review. Epilepsia 1973, 14: 277-310

2. Childress S.J. and Gluckman M.I. 1,4- Benzodiazepines. Journal of Pharmaceutical Sciences. 1964; 53, 6: 577-590

3. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 1990; 8th Edition, Pergamon Press:1668

4. MacDonald A., Michaelis A.F., and Senkowski B.Z. Chlordiazepoxide Hydrochloride. APDS, 2:39-51

5. Morillo A., Revzin A.M. and Knauss T. Physiological Mechanisms of Action of Chlordiazepoxide in Cats. Psychopharmacologia 1962; 3: 386-394

6. Randall L.O., Scheckel C.L. and Banziger R.F. Pharmacology of the Metabolites of Chlordiazepoxide and Diazepam. Current Therapeutic Research. 1965; 7, 9: 590-600

7. Rickels K., Baumm C., Raab E., Taylor W. and Moore E. A Psychopharmacological Evaluation of Chlordiazepoxide, LA-1 and Placebo, Carried out with Anxious, Neurotic Medical Clinic Patients. Medical Times 1965; 93, No.3: 238-245

8. Rose J.T. Phenoxypropazine and Chlordiazepoxide in Depression. Clinical Notes; 1964, 8: 899-900

9. Rudy B.C. and Senkowski B.Z. Clidinium Bromide.

APDS, 2: 145-161

10. Schaller W., Zabransky F. and Kuehn A. Effects of Benzodiazepines on Central Nervous System of Cat. Arch Int Pharmacodyn 1964; 149, 3-4: 467-483

11. Shader R.I., Greenblatt D.J., Salzman C., Kochansky G.E. and Harmatz J.S.Benzodiazepines: Safety and Toxicity. NEJM 1975; 288: 23-26

12. Tobin J.M. and Lewis N.D.C. New Psychotherapeutic Agent, Chlordiazepoxide. JAMA 1960, 5: 1242-1249

13. USP DI Drug Information for the Health Care Professional. 1993; 1: 811-812

14. Zbinden G., Bagdon R.E., Keith E.F., Phillips R.D. and Randall L.O. Experimental and Clinical Toxicology of Chlordiazepoxide (Librium). Toxicology and Applied Pharmacology 1961; 3: 619-637

15. Zbinden G. and Randall L.O. Pharmacology of Benzodiazepines: Laboratory and Clinical Correlations. Advances in Pharmacology; 1967,5: 213-291