**LIBRIUM® (chlordiazepoxide HCl)**

**CAPSULES**

**DESCRIPTION:** Librium, the original chlordiazepoxide HCl and prototype for the benzodiazepine compounds, was synthesized and developed at Hoffmann-La Roche Inc. It is a versatile therapeutic agent of proven value for the relief of anxiety. Librium is among the safer of the effective psychopharmacologic compounds available, as demonstrated by extensive clinical evidence.

Librium is available as capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Each capsule also contains corn starch, lactose and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dyes: 5-mg capsules — FD&C Blue No. 1 and FD&C Yellow No. 6 plus D&C Yellow No. 10 and either FD&C Blue No. 1 or FD&C Green No. 3; 10-mg capsules — FD&C Yellow No. 10 and either FD&C Blue No. 1 plus FD&C Red No. 3 or FD&C Green No. 3 plus FD&C Red No. 40; 25-mg capsules — FD&C Yellow No. 10 and either FD&C Green No. 3 or FD&C Blue No. 1.

Chlordiazepoxide hydrochloride is 7-chloro-2-(methylamino)-5-phenyl-1,4-benzodiazepine 4-oxide hydrochloride. A white to practically white crystalline substance, it is soluble in water. It is unstable in solution and the powder must be protected from light. The molecular weight is 336.22. The structural formula of chlordiazepoxide hydrochloride is as follows:

![Chemical Structure Diagram]

**CLINICAL PHARMACOLOGY:** Librium (chlordiazepoxide HCl) has anxiolytic, sedative, appetite-stimulating and weak analgesic actions. The precise mechanism of action is not known. The drug blocks EEG arousal from stimulation of the brain. The drug dosage which effectively blocked the taming effect of chlordiazepoxide HCl was further demonstrated in many species of animals and these studies are suggestive of action on the limbic system of the brain, which recent evidence indicates is involved in emotional responses.

Hostile monkeys were made tame by oral drug doses which contained methyl and propyl parabens and potassium sorbate, with the following dyes: 5-mg capsules — FD&C Blue No. 1 and FD&C Yellow No. 6 plus D&C Yellow No. 10 and either FD&C Blue No. 1 or FD&C Green No. 3; 10-mg capsules — FD&C Yellow No. 10 and either FD&C Blue No. 1 plus FD&C Red No. 3 or FD&C Green No. 3 plus FD&C Red No. 40; 25-mg capsules — FD&C Yellow No. 10 and either FD&C Green No. 3 or FD&C Blue No. 1.

Animal Pharmacology: The drug has been studied extensively in many species of animals and these studies are suggestive of action on the limbic system of the brain, which recent evidence indicates is involved in emotional responses.

![Drug Effect Diagram]

**EFFECTS ON REPRODUCTION:**

Librium affected the fertility of off-spring which may be attributable to sedative activity, thus resulting in lack of interest in mating and lengthened maternal nursing and care of the young. One neonate in each of the first and second matings in the rat reproduction study at the 100 mg/kg dose exhibited major skeletal defects. Further studies are in progress to determine the significance of these findings.

**INDICATIONS AND USAGE:** Librium is indicated for the management of anxiety disorders or for the short term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The effectiveness of Librium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.

**CONTRAINDICATIONS:** Librium is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** Chlordiazepoxide HCl may impair the mental and physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. Similarly, it may impair mental alertness in children. Use of alcohol or other central nervous system depressants may have an additive effect. Patients should be warned accordingly.

**Usage in Pregnancy:** An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, their use during this period should always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

Withdrawal symptoms of the barbiturate type have occurred following the discontinuation of benzodiazepines. (See DRUG ABUSE AND DEPENDENCE section.)

**PRECAUTIONS:** In elderly and debilitated patients, it is recommended that the dosage be limited to the smallest effective amount to permit gradual titration of the drug and to prevent potential adverse reactions. The dosage used in the treatment of anxiety states where there is any evidence of impending depression; it should be borne in mind that suicidal tendencies may be present and protective measures may be necessary. Although clinical studies have not established a cause and effect relationship, physicians should be aware that variable effects on blood coagulation have been reported very rarely in patients receiving oral anticoagulants and Librium. In view of isolated reports associating chlordiazepoxide with exacerbation of porphyria, caution should be exercised in prescribing chlordiazepoxide to patients suffering from this disease.

Paradoxical reactions, eg excitement, stimulation and acute rage, have been reported in psychiatric patients and in hyperactive aggressive pediatric patients, and should be watched for during Librium therapy. The usual precautions are indicated when Librium is used in the treatment of anxiety states where there is any evidence of impending depression; it should be borne in mind that suicidal tendencies may be present and protective measures may be necessary. Although clinical studies have not established a cause and effect relationship, physicians should be aware that variable effects on blood coagulation have been reported very rarely in patients receiving oral anticoagulants and Librium. In view of isolated reports associating chlordiazepoxide with exacerbation of porphyria, caution should be exercised in prescribing chlordiazepoxide to patients suffering from this disease.

**Pediatric Use:** Because of the varied response of pediatric patients to CNS-acting drugs, therapy should be initiated with the lowest dose and increased as required (see DOSAGE AND ADMINISTRATION). Since clinical experience with Librium in pediatric patients is limited, the low end of the recommended age and weight range for this age group is not recommended. Hyperactive aggressive pediatric patients should be monitored for paradoxical reactions to Librium (see PRECAUTIONS).
The necessity of discontinuing Chlordiazepoxide. Because of the wide range of clinical indications for Librium, the optimum dosage varies with the diagnosis and response of the individual patient. The dosage, therefore, should be individualized for maximum beneficial effects.

ADVERSE REACTIONS: The necessity of discontinuing therapy because of undesirable effects has been rare. Drowsiness, ataxia and confusion have been reported in some patients – particularly the elderly and debilitated. While these effects can be avoided in almost all instances by proper dosage adjustment, they have occasionally been observed at the lower dosage ranges. In a few instances, syncope has been reported.

Other adverse reactions reported during therapy include isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, as well as increased and decreased libido. Such side effects have been infrequent, and are generally controlled with reduction of dosage. Changes in EEG patterns (low-voltage fast activity) have been observed in patients during and after Librium treatment. Blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have occasionally been reported during therapy. When Librium treatment is protracted, periodic blood counts and liver function tests are advisable.

DRUG ABUSE AND DEPENDENCE: Chlordiazepoxide hydrochloride capsules are classified by the Drug Enforcement Administration as a Schedule IV controlled substance. Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating), have been reported following abrupt discontinuance of Chlordiazepoxide. The more severe withdrawal symptoms have usually been noted in those patients who had received excessive doses over an extended period of time. Generally, milder withdrawal symptoms (eg, dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines administered continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed. In the experience with the use of Librium, patients have occasionally been observed to suffer from withdrawal symptoms when receiving chlorpromazine or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE: Manifestations of Librium overdosage include somnolence, confusion, coma and diminished reflexes. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdose, although, in general, these effects have been minimal following Librium overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of Levophed® (norepinephrine) or Aramine (metaraminol). Dialysis is of limited value. There have been occasional reports of excitation in patients following chlorzepoxide HCI overdosage; if this occurs barbiturates should not be used. As with the management of intentional overdose with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and other agents. Flumazenil should be administered to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for reexcitation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizures in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert must be consulted prior to use.

DOSAGE AND ADMINISTRATION: Because of the wide range of clinical indications for Librium, the optimum dosage varies with the diagnosis and response of the individual patient. The dosage, therefore, should be individualized for maximum beneficial effects.

ADULTS

<table>
<thead>
<tr>
<th>USUAL DAILY DOSE</th>
<th>Doses</th>
<th>Times daily</th>
</tr>
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<tbody>
<tr>
<td>Relief of Mild and Moderate Anxiety Disorders and Symptoms of Anxiety</td>
<td>20 mg</td>
<td>3 or 4 times daily</td>
</tr>
<tr>
<td>Relief of Severe Anxiety Disorders and Symptoms of Anxiety</td>
<td>50 mg or 100 mg IM* 1 hour prior to surgery</td>
<td></td>
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<tr>
<td>Geriatric Patients, or in the presence of debilitating disease</td>
<td>5 mg or 10 mg</td>
<td>2 to 4 times daily</td>
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PEDiatric PATIENTS

<table>
<thead>
<tr>
<th>USUAL DAILY DOSE</th>
<th>Doses</th>
<th>Times daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Because of the varied response of pediatric patients to CNS-acting drugs, therapy should be initiated with the lowest dose and increased as required. Since clinical experience in pediatric patients under 6 years of age is limited, the use of the drug in this age group is not recommended.</td>
<td>5 mg</td>
<td>2 to 4 times daily (may be increased in some pediatric patients to 10 mg, 2 to 3 times daily)</td>
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</tbody>
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HOW SUPPLIED: Librium (chlordiazepoxide HCI) Capsules are available in the following presentations:

- 5 mg hard gelatin capsules in bottles of 100 (NDC-0187-3750-10), with Librium 5 imprinted on the opaque green cap and ICN imprinted on the opaque green body.
- 10 mg hard gelatin capsules in bottles of 100 (NDC-0187-3751-10), with Librium 10 imprinted on the opaque black cap and ICN imprinted on the opaque green body.
- 25 mg hard gelatin capsules in bottles of 100 (NDC-0187-3758-10), with Librium 25 imprinted on the opaque green cap and ICN imprinted on the opaque white body.

* See package insert for Injectable Librium (chlordiazepoxide HCI).

Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).