For the use of a Registered Medical Practitioner only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see Warnings, Drug Interactions].
• Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required.
• Follow patients for signs and symptoms of respiratory depression and sedation.

1. Generic Name and Brand Name

Chlordiazepoxide Tablets I.P. 5 mg
Librium® 5

2. Qualitative and Quantitative Composition:

Each film coated tablet contains:
Chlordiazepoxide I.P. …… 5 mg
Excipients…….q.s.
Colours: Indigo Carmine Aluminum Lake and Ferric Oxide USP NF Yellow

3. Dosage Form & strength

Refer section 1 and 2.

4. Clinical particulars

4.1 Therapeutic indication

Management of Anxiety disorders or for the short-term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety.

4.2 Posology and method of administration

Relief of Mild and Moderate Anxiety Disorders and Symptoms of Anxiety: 5 mg or 10 mg, 3 or 4 times daily
Geriatric Patients, or in the presence of debilitating disease.: 5 mg, 2 to 4 times daily
Symptomatic relief of acute alcohol withdrawal- 25 to 100 mg and repeated if necessary in 2 to 4 hours.
Preoperative Apprehension and Anxiety: On days preceding surgery, 5 to 10 mg orally, 3 or 4 times daily.

Pediatric Patients
5 mg, 2 to 4 times daily (may be increased in some pediatric patients to 10 mg, 2 to 3 times daily)
The use of the drug for pediatric patients under 6 years of age is not recommended. Therapy should be initiated with the lowest dose and increased as required

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Concomitant use of benzodiazepines, including Librium, and opioids may result in profound sedation, respiratory depression, coma, and death. In patients already receiving an opioid analgesic, prescribe a lower initial dose of Librium than indicated in the absence of an opioid and titrate based on clinical response.

Driving & using Machines -Chlordiazepoxide hydrochloride may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery.

Usage in Pregnancy: 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 as increased risk of congenital malformations is associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy.

In elderly and debilitated patients - It is recommended that the dosage be limited to the smallest effective amount to preclude the development of ataxia or over sedation (10 mg or less per day initially, to be increased gradually as needed and tolerated).

Pediatric Use: Chlordiazepoxide hydrochloride in pediatric patients under 6 years is not recommended. Hyperactive aggressive pediatric patients should be monitored for paradoxical reactions to Chlordiazepoxide hydrochloride.

Nursing Mothers: Due to the lack of conclusive safety data, use in nursing mothers is not recommended.

4.5 Drug Interactions

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABAA sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids and monitor patients closely for respiratory depression and sedation.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

Pregnancy:
Chlordiazepoxide crosses the placenta.
There is a limited amount of data from the use of chlordiazepoxide in pregnant women.

Studies in animals have shown reproductive toxicity.
Librium should not be used during pregnancy, especially during the first and last trimester unless the clinical condition of the woman requires treatment with chlordiazepoxide. If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician to discuss discontinuation of Librium if she intends to become or suspects that she is pregnant.
The administration of high doses or prolonged administration of low doses of benzodiazepines in the last trimester of pregnancy or during labor have been reported to produce irregularities in the foetal heart rate, moderate respiratory depression, hypotonia, poor sucking and hypothermia in the neonate. Moreover, infants born to mothers who chronically took benzodiazepines during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.
Breast-feeding:
Chlordiazepoxide may appear in breast milk. If possible, the use of Librium should be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medications of this type, Librium may modify patients performance at skilled tasks. Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or use machinery. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients should further be advised that alcohol may intensify any impairment, and should, therefore, be avoided during treatment.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988.
When prescribing this medicine, patients should be told:
• The medicine is likely to affect your ability to drive
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely

4.8 Undesirable effects

SIDE EFFECTS: Reported side effects include:

CNS: Drowsiness, ataxia and confusion, dizziness has been reported in some patients particularly the elderly and debilitate, Movement disorders, extrapyramidal symptoms, Changes in EEG patterns (low-voltage fast activity)
Gastrointestinal: Nausea, constipation, liver dysfunction, jaundice
Musculoskeletal: Impaired muscle control

Skin: Rash, eruptions, edema
Reproductive: Minor menstrual irregularities, Decreased desire for sexual activity (decreased libido).
Blood: blood dyscrasias including agranulocytosis
CVS: Changes in EEG patterns (low-voltage fast activity) have been observed in patients during and after Librium treatment.

DRUG ABUSE AND DEPENDENCE:
Chlordiazepoxide hydrochloride capsules are classified 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 occurred after abrupt discontinuance of chlordiazepoxide.
They may be seen in those patients who had received excessive doses over an extended period of time.
Addiction-prone individuals (such as drug addicts or alcoholics) must be under careful surveillance when receiving chlordiazepoxide or, other, psychotropic agents because of the predisposition of such patients to habituation and dependence.

4.9 Overdose and Management

Symptoms: Manifestations of chlordiazepoxide over-dosage includes somnolence, con-fusion, coma and diminished re-flexes. Respiration, pulse, and blood pressure should be monitored, as in all cases of drug overdosage, although, in general, these effects have been minimal following chlordiazepoxide overdosage. General supportive measures should be employed, along with immediate gastric ravage. Intravenous fluids should be administered, and an adequate airway maintained. Hypotension may be combated using norepinephrine or metaraminol. Dialysis is of limited value. There have been occasional reports of excitation in patients following chlordiazepoxide overdosage; if this occurs barbiturates should not be used.

Management
As with the management of intentional overdosage 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 may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intra-venous 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 re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant over-dose.

5. Pharmacological properties

5.1 Mechanism of action

Chlordiazepoxide is a psychotropic substance from the class of 1,4-benzodiazepines with tension, excitement, anxiety attenuating properties and sedative and hypnotic effects. Chlordiazepoxide shows muscle relaxant and anticonvulsant effects.

Chlordiazepoxide has a low affinity as an agonist at specific benzodiazepine receptors located on GABA-ergic neurons. Stimulation of benzodiazepine receptors potentates the actions of GABA. GABA-ergic neurons are inhibitory in the nervous system. This results in diminution of various 5-HT, dopamine and noradrenergic neurotransmitter system effects.

5.2 Pharmacodynamic Properties

Chlordiazepoxide hydrochloride has antianxiety, sedative, appetite-stimulating and weak analgesic actions. The drug blocks EEG arousal from stimulation of the brain stem reticular formation.
Animal studies are suggestive of action on the limbic system of the brain, which recent evidence indicates is involved in emotional responses.

5.3 Pharmacokinetic properties
Absorption:

Librium is well absorbed, with peak blood levels being achieved one or two hours after administration. Steady-state levels are usually reached within three days.

Distribution:

Chlordiazepoxide is metabolized to desmethyl-chlordiazepoxide. Demoxepam and desmethyl diazepam are also found in the plasma of patients on continuous treatment. The active metabolite desmethyl-chlordiazepoxide has an accumulation half-life of 10 – 18 hours; that of demoxepam has been recorded as 21 – 78 hours.

Steady-state levels of these active metabolites are reached after 10-15 days, with metabolite concentrations which are similar to those of the parent drug.

Elimination: The drug has a half-life is of 6 - 30 hours.
Metabolites: Demoxepam: 14–95 hours.
Desmethyl chlordiazepoxide: 18 hours.
Desmethyl diazepam: 30–200 hours.
Oxazepam: 3–21 hours

Pharmacokinetic / pharmacodynamic relationship:
No clear correlation has been demonstrated between the blood levels of Librium and its clinical effects.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Mutagenic and tumorigenic potential:

In in-vivo and in-vitro studies with chlordiazepoxide, there are indications for a mutagenic effect. Nevertheless, in similar test systems results are negative. The relevance of the positive findings is currently unclear.
In carcinogenicity studies in mice an increase of liver tumours was seen at high doses, especially in males, whereas no increase of tumour incidence was seen in rats.

Reproductive toxicity:

In animal studies increased resorption rates, increased incidence of stillbirth and neonatal death, malformation of the scull (exencephaly, cleft palate), lung anomalies and changes in the urogenital tract as well as behavioural disorders and neurochemical changes have been observed in the offspring.

7. Description

Librium 5 is supplied for oral administration, as film coated tablet of Chlordiazepoxide. Each film coated tablet of Librium 5 contains Chlordiazepoxide 500 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage and handling instructions

Refer Pack

9. Patient Counseling Information

- Advice not to drive, operate heavy machinery, or do other dangerous activities
- Advice not to stop Librium suddenly, you may have withdrawal symptoms. It should be slowly stopped to avoid withdrawal symptoms.
- Advise both patients and caregivers about the risks of respiratory depression and sedation when Librium is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use with the opioid have been determined.
- Chlordiazepoxide HCl may impair the mental and/or 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. The concomitant use of

alcohol or other central nervous system depressants may have an additive effect. PATIENTS SHOULD BE WARNED ACCORDINGLY.

- 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.

Information for Patients

- To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

10. Details of manufacturer

Manufactured By
Abbott Healthcare Private Limited
Village Bhatauli Khurd, PO: Baddi –173 205,
Dist: Solan, Himachal Pradesh, India.
® Regd. Trade Mark of Abbott Healthcare Pvt. Ltd.

11. Details of permission or licence number with date

Refer Pack for Permission/License Details

12. Date of revision

Version No. 1.0, dated 01/11/2023

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com