Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Librium 5mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 5mg chlordiazepoxide hydrochloride.

Excipients: Each capsule contains 105.9 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard. (Capsule)

Size no. 4, opaque hard gelatin capsules having a yellow body and a green cap, imprinted with the monogram 'LIB 5' in red-brown and containing a white to off-white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Short-term (2-4 weeks) symptomatic treatment of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.

2. In the control of muscle spasm.

3. In the management of alcohol withdrawal.

4.2 Posology and method of administration

Posology

Anxiety
Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 4 weeks, including a tapering off process.

In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise. Little is known regarding the efficacy or safety of benzodiazepines in long-term use. Long-term chronic use is not recommended.

Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged period may require a longer period during which doses are reduced. Specialist help may be appropriate.

Adults

Anxietystatesincludingmusclespasms:
The usual total daily dosage is up to 30mg in divided doses. In severe cases this may be increased to a total daily dosage of 40 to 100 mg in divided doses.

Managementofsymptomsofalcoholwithdrawal:
The usual dosage is 25 to 100 mg repeated in 2 to 4 hours if necessary.

Paediatric population
Not for paediatric use. Use in children is not recommended due to insufficient clinical data.

Special patient groups:
Elderly or debilitated patients, patients with organic brain damage, respiratory impairment and/or hepatic or severe renal dysfunction should normally not exceed half the usual daily dosage.

Method of administration
For oral use.
To be swallowed with water.

4.3 Contraindications

Librium is contraindicated in:

- Hypersensitivity to the active substance chlordiazepoxide or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Severe pulmonary insufficiency
- Respiratory depression
- Sleep apnoea syndrome
- Severe hepatic insufficiency
- Spinal or cerebral ataxia

4.4 Special warnings and precautions for use

Risk from concomitant use of opioids:
Concomitant use of Librium and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Librium with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Librium concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Tolerance
Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence
Use of benzodiazepine may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse, or in patients with a history of severe personality disorder. Therefore, caution is required in patients with dependency history.

Once physical dependence has developed, a sudden termination of treatment results in withdrawal symptoms e.g. depression, headache, muscle pain, muscle weakness, nervousness, extreme anxiety, tension, restlessness, confusion, mood changes, rebound insomnia, sweating, diarrhoea and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and paresthesias of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Abuse of benzodiazepines has been reported.

Reboundinsomniaandanxiety
This is a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

Durationof treatment
The duration of treatment should be as short as possible (see section 4.2 Posology) depending on the indication, but should not exceed 4 weeks, including tapering off process. Routine repeat prescriptions should be avoided. Extension beyond these periods should not take place without re evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia
Amnesia may occur. Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-
8 hours (see section 4.8 Undesirable effects).

Psychiatricand'paradoxical'reactions
Treatments with benzodiazepines may cause psychiatric as well as 'paradoxic' reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour, other adverse behavioural effects, unmask of depressions with suicidal tendencies and other negative behavioural disorders are known to occur when using benzodiazepines. Should this occur, use of the product should be discontinued.

They are most likely to occur in children and in elderly patients.

Specific patientgroups
Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.

Elderly patients should be given a reduced dose (see section 4.2 Posology). Due to myorelaxant effect of Librium there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy and reduced doses should be given to patients with severe renal or hepatic disease.

Benzodiazepines are not recommended for the primary treatment of psychotic illness, phobia or obsessive-compulsive diseases.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression since it may uncover depression with suicidal tendencies. Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. Extreme caution should be used in prescribing benzodiazepines to patients with personality disorders.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Librium.

4.5 Interaction with other medicinal products and other forms of interactions

Opioids:
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Librium with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

Concomitant intake with alcohol should be avoided. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

If Librium is combined with centrally-acting drugs, enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychic dependence. Elderly patients require special supervision.

Librium in combination with 4-hydroxybutanoic (sodium oxybate) may cause an increased respiratory depression.

Concurrent treatment with tranquilizers may increase the effects of relaxing the muscles, especially elderly patients receiving higher doses of Librium should be well monitored (higher risk of falling).

When Librium is used in conjunction with anti-epileptic drugs, side effects and toxicity may be more evident, particularly with hydantoins or barbiturates or combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Compounds which inhibit hepatic enzymes e.g. cimetidine, omeprazole, macrolide antibiotics (erythromycin) and disulfiram have been shown to reduce the clearance of benzodiazepines and may potentiate their action. The same applies to the use of contraceptive agents. Known inducers of hepatic enzymes e.g. rifampicin, may increase the clearance of benzodiazepines.

In patients receiving long-term treatment with other medicines (such as centrally acting antihypertensive agents, beta receptor blockers, anticoagulant agents and cardiac glycosides), the nature and extent of interactions cannot safely be foreseen.

4.6 Fertility, pregnancy and lactation

Pregnancy
Chlordiazepoxide crosses the placenta.
Benzodiazepines should only be used during pregnancy or lactation if considered essential by the physician. Animal studies with benzodiazepines have shown minor effects on the foetus while a few studies have reported late behavioural disturbance in offspring exposed in utero.

Librium should not be used during pregnancy, especially in 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 labour, have been reported to produce irregularities fetal heart rate, hypothermia, hypotonia, respiratory depression and poor sucking (floppy infant syndrome) in the neonate. Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Breast-feeding
Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

4.7 Effects on ability to drive and use machines

Patients should be advised that benzodiazepines may modify performance of skilled tasks. Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also section 4.5 Interactions). Patients are also advised that alcohol may intensify any impairment, and therefore alcohol should be avoided during treatment.

4.8 Undesirable effects

Common adverse effects include sedation, dizziness, somnolence, ataxia, fatigue and balance disorder. These adverse effects are dose-related and may persist into the following day even after a single dose. However, these phenomena occur

predominantly at the start of therapy and usually disappear with repeated administration. Elderly patients are particularly sensitive to the effects of centrally-depressant drugs and may experience confusion, especially if organic brain changes are present.

Evaluation of undesirable effects is based on the following frequency information:

- Very common (> 1/10)
- Common (> 1/100 to < 1/10)
- Uncommon (> 1/1,000) to < 1/100)
- Rare (> 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (Frequency cannot be estimated from the available data)

Organ class	Common	Rare	Not known
Blood and lymphatic system		Bone marrow depression (e.g. thrombocytopenia, leucopoenia, agranulocytosis, pancytopenia)	
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders			Increased appetite
Psychiatric disorders			Amnesia, * Hallucinations, Dependence, Depression, ** Restlessness, Agitation, Irritability, Depressed level of consciousness, Aggression, Delusion, Nightmares, Psychotic disorder, Abnormal behaviour, Emotional disturbances, Paradoxical drug reaction (e.g. anxiety, sleep disorders, insomnia, suicide attempt, suicidal ideation
Nervous system disorders	Sedation, Dizziness, Somnolence, Ataxia, Balance disorder, Confusional state	Headache, Vertigo	Dysarthria, Gait disturbance, Extrapyramidal disorder (e.g. tremor, dyskinesia)
Eye disorders		Visual impairment incl. diplopia	
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders			Respiratory depression
Gastrointestinal disorders		Gastrointestinal disorder	

Hepatobiliary disorders			Jaundice, Blood bilirubin increased, Transaminases increased, Blood alkaline phosphatase increased
Skin and subcutaneous tissues disorders		Skin reaction (e.g. rash)	
Musculoskeletal and connective tissue disorders			Muscular weakness
Renal and urinary disorders		Urinary retention	
Reproductive system and breast disorders		Libido disorder, Erectile dysfunction, Menstrual disorder	
General disorders and administration site conditions	Fatigue		

** Anterograde amnesia may occur at therapeutic doses, with increasing risk at higher doses. This may be associated with inappropriate behaviour (see section 4.4)*
*** Pre-existing depression may be unmasked by benzodiazepines.*

Reaction like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepine-like agents. They may be quite severe with this product. They are more likely to occur in children and elderly patients.

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in the withdrawal or rebound phenomena. Psychological dependence may occur. Abuse of benzodiazepines has been reported.

Unsteadiness, changes in salivation and incontinence may occur.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

As with other benzodiazepines, overdose with chlordiazepoxide alone should not present a threat to life unless combined with other CNS depressants (including alcohol).

Signs and symptoms
Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Treatment
Treatment should be mainly symptomatic (stabilizing of circulatory function, monitoring). In mild cases patients should sleep under control of respiratory and circulatory function. Induced vomiting is not recommended. The benefit of gastric decontamination is uncertain. Activated charcoal (charcoal dose: 50 g for an adult, 1 g/kg for a child) may be considered in adults or children who have taken more than a potentially toxic amount within 1 hour, provided the airway can be protected. Gastric lavage is not necessary after small to moderate ingestions if activated charcoal can be given promptly, but may be done in severe cases. Due to the high protein binding and the high volume of distribution of chlordiazepoxide forced diuresis or

hemodiuresis seem to be of small value. Flumazenil, a benzodiazepine antagonist, is available but should rarely be required. It may be required in children who are naive to benzodiazepines or for accidental overdose of benzodiazepines during procedural sedation. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil should not normally be used in patients with a history of seizures, head injury, chronic benzodiazepine use, co-ingestion of a benzodiazepine or a pro-convulant (e.g. tricyclic antidepressant).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptica, anxiolytics, benzodiazepines derivatives
ATC code: N05BA02

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 the muscle relaxant and anticonvulsant effects.

Chlordiazepoxide binds to specific benzodiazepine receptors located on the GABA-ergic neurons and potentiates the inhibitory actions of GABA-ergic neurons in the nervous system. After prolonged benzodiazepine treatment development of tolerance has been observed. Chronic benzodiazepine use leads to compensating changes in the central nervous system. $GABA_A$ receptors may become less responsive to the continuing acute effects of benzodiazepines either as a result of adaption in the $GABA_A$ receptor itself, intracellular mechanisms, or changes in the neurotransmitter systems. Probably multiple adaptive mechanisms simultaneously coexist.

An increase in intensity and incidence of CNS toxicity with age has been observed especially at high doses. Therefore, the initial dose of Librium in elderly patients should be decreased (see section 4.2 Posology). The increased CNS toxicity in elderly patients seems to be the result of a combination of pharmacokinetic and pharmacodynamic factors.

5.2 Pharmacokinetic properties

Absorption
Librium is well absorbed, with peak blood levels being achieved 1 or 2 hours after administration. The drug has a half life of 6 - 30 hours. Steady-state levels are usually reached within 3 days.

Distribution
Chlordiazepoxide is metabolised to desmethylchlordiazepoxide. Demoxepam and desmethyldiazepam are also found in the plasma of patients on continuous treatment. The active metabolite desmethylchlordiazepoxide 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.

No clear correlation has been demonstrated between the blood levels of Librium and its clinical effects.

5.3 Preclinical safety data

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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Maize starch
Talc
Lactose monohydrate
Yellow iron oxide (E172)
Indigo carmine (E132)
Titanium dioxide (E171)
Quinoline yellow (E104)
Erythrosine (E127)
Red Iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Amber glass screw cap bottle (100 capsules).

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

PA2010/041/001

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