SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlordiazepoxide capsules BP 10 mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Chlordiazepoxide hydrochloride BP 10.00 mg.

Excipient with known effect:
Each capsule contains 173 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

The product is presented in the form of size 4, dark green opaque/chocolate brown opaque capsules printed with CDZ 10 and company logo.

4.1 Therapeutic indications

Relief of anxiety: Benzodiazepines are indicated for the 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.

Insomnia: Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

Symptomatic relief of acute alcohol withdrawal.

Muscle spasm of varied aetiology.

4.2 Posology and method of administration

Posology:

Anxiety states: Usual dose 10 mg, 2-3 times a day and up to 30 mg daily in divided doses. For severe symptoms 20 mg, 2-4 times a day. Maximum dose up to 100 mg daily in divided doses. Adjusted on an individual basis.

Generally, duration of treatment should not be more than 4 weeks, including a tapering-off process.

Insomnia associated with anxiety:
10 to 30 mg before retiring. Generally, duration of treatment varies from a few days to two weeks, with a maximum including a tapering-off process of four weeks.

Symptomatic relief of acute alcohol withdrawal:
25 to 100 mg and repeated if necessary in 2 to 4 hours.

Muscle spasm of varied aetiology:
10 to 30 mg daily in divided doses.

Paediatric patients
Chlordiazepoxide is not for paediatric use.

Special patient groups
Elderly or debilitated patients, patients with organic brain damage, respiratory impairment and/or hepatic or renal dysfunction should normally not exceed half of the doses normally recommended.

The lowest dose which can control symptoms should be used. The dosage and duration of treatment should be determined on an individual basis dependent by the patient's response and severity of the disorder. Given that chlordiazepoxide is a long-acting benzodiazepine, the patient should be monitored regularly at the start of the treatment to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

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. Treatment should not be continued at the full dose beyond four weeks.

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 time may require a longer period during which doses are reduced. Specialist help may be appropriate.

Method of administration
Chlordiazepoxide capsules are for oral administration and must be taken with water and not be chewed.

4.3 Contraindications

Chlordiazepoxide Capsules are contraindicated for patients with:
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Myasthenia gravis
Severe pulmonary insufficiency
Respiratory depression

Severe hepatic insufficiency
Sleep apnoea syndrome
Phobic or obsessional states
Chronic psychosis
Spinal or cerebral ataxia

4.4 Special warnings and precautions for use

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

Dependence and withdrawal
The dependent potential of the benzodiazepines is low, particularly when limited to short-term use. Risk for physical and psychological dependence increases when high doses are used, especially when given over long periods. This is particularly so in patients with a history of alcoholism or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential. Routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Symptoms such as headaches, muscle pain, extreme anxiety, restlessness, confusion, depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea have been reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time. In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations, psychotic manifestations or epileptic seizures.

Abuse of benzodiazepines has been reported.

Rebound insomnia and anxiety
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.

Duration of 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.

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 (also see section 4.8 Undesirable effects).

Psychiatric and paradoxical reactions
Rare behavioural effects including restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should these effects occur, use of the medicinal product should be discontinued. They are more likely to occur in children and the elderly.

Risk from concomitant use of opioids:

Concomitant use of chlordiazepoxide and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe chlordiazepoxide 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).

Specific patient groups
Elderly patients should be given a reduced dose (see section 4.2). A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are contraindicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy and reduced doses should be given to patients with renal or hepatic disease.

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

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

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

Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

If chlordiazepoxide is combined with centrally-acting drugs such as neuroleptics, tranquilisers, antidepressants, hypnotics, analgesics, anaesthetics, and sedative antihistamines the central depressive effects are likely to be intensified. In the case of narcotic analgesics, enhancement of the euphoria may also occur leading to an increase in psychic dependence. The elderly require special supervision.

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

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

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

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

The concomitant use of sedative medicines such as benzodiazepines 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).

Known inhibitors of hepatic enzymes *e.g.* cimetidine, omeprazole, macrolide antiobiotics (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), nature and extent of interactions cannot safely be foreseen.

Benzodiazepines possibly antagonise the effect of levodopa.

Sedative effects are possibly increased when benzodiazepines are given with moxonidine.

Benzodiazepines enhance effects of sodium oxybate. Concomitant use should be avoided.

Effects of benzodiazepines are possibly reduced by theophylline.

4.6 Fertility, pregnancy and lactation

Contraception in males and females:

Due to the genotoxic potential of Chlordiazepoxide (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with Chlordiazepoxide and for 7 months following completion of treatment.

If the patient suspects to be pregnant or intends to become pregnant, she should be warned to contact her physician to discuss discontinuation of Chlordiazepoxide.

Men are recommended to use effective contraceptive measures and to not father a child while receiving Chlordiazepoxide and for 4 months following completion of treatment.

Pregnancy:
Chlordiazepoxide crosses the placenta.
There islimited amount of data from the use of chlordiazepoxide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Chlordiazepoxide 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 doctor to discuss discontinuation of chlordiazepoxide 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 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 chlordiazepoxide should be avoided during breastfeeding.

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medicaments of this type, chlordiazepoxide 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

Common adverse effects include drowsiness, sedation, dizziness, somnolence, fatigue, balance disorder, unsteadiness and ataxia; these 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. The elderly are particularly sensitive to the effects of centrally-depressant drugs and may experience confusion, especially in the presence of organic brain changes; and the dosage of chlordiazepoxide should not exceed one-half that recommended for other adults.

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 available data).

Blood and lymphatic system disorders:

Rare: Bone marrow depression (*e.g.* thrombocytopenia, leukopenia, agranulocytosis, pancytopenia).

Immune system disorders:

Very rare: Anaphylactic reactions, angioedema.

Frequency not known: Hypersensitivity.

Metabolism and nutrition disorders:

Frequency not known: Increased appetite.

Psychiatric disorders:

Frequency not known: 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:

Common: sedation, dizziness, unsteadiness, somnolence, ataxia, balance disorder, confusional states.

Rare: Headache, vertigo.

Frequency not known: Dysarthria, gait disturbance, extrapyramidal disorder (*e.g.* tremor, dyskinesia).

Eye disorders:

Rare: Visual impairment including diplopia.

Vascular disorders:

Rare: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Frequency not known: Respiratory depression.

Gastrointestinal disorders:

Rare: Gastrointestinal upsets.

Hepatobiliary disorders:

Frequency not known: Jaundice, blood bilirubin increased, transaminases increased, blood alkaline phosphatase increased.

Skin and subcutaneous tissue disorders:

Rare: Skin reaction (*e.g.* rash).

Musculoskeletal and connective tissue disorders:

Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly.

Frequency not known: Muscle weakness.

Renal and urinary disorders:

Rare: Urinary retention, incontinence.

Reproductive system and breast disorders:

Rare: Libido disorders, erectile dysfunction, menstrual disorder.

General disorders and administration site conditions:

Common: Fatigue.

Frequency not known: Changes in salivation.

Amnesia
Anterograde amnesia may occur at the therapeutic doses, with increasing risk at higher doses. This may be associated with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may be unmasked by benzodiazepines.

Psychiatric and paradoxical reactions
Reactions 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 the elderly.

Dependence
Use (even 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

When taken alone in overdosage, chlordiazepoxide presents few problems in management. When taken with centrally-acting drugs, especially alcohol, the effects of overdose are likely to be more severe and in the absence of supportive measures may prove fatal.

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.

Management:
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

Treatment is symptomatic.
The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for an adult, 1 g/kg for a child) in adults or children who have taken more than a potentially toxic amount within 1 hour, provided the airway can be protected.

The value of dialysis has not been determined. Flumazenil, a benzodiazepine antagonist, is available but should rarely be required. It may be required in children

who are naïve to benzodiazepines or patients with chronic obstructive pulmonary disease (COPD) as an alternative to ventilation. 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 and tricyclic antidepressant or other proconvulsant.

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, anxiolytics, benzodiazepine derivatives, ATC code: N05BA02

Chlorodiazepoxide 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 low affinity as an agonist at specific benzodiazepine receptors located on gama-aminobutyric acid (GABA)-ergic neurones. Stimulation of benzodiazepine receptors potentates the actions of GABA. GABA-ergic neurones are inhibitory in the nervous system. This results in diminution of various 5-HT, dopamine and noradrenergic neurotransmitter system effects.

5.2 Pharmacokinetic properties

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

Distribution
Chlordiazepoxide is metabolised to desmethylchlordiazepoxide. Demoxepam and desmethlydiazepam 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.

Pharmacokinetic / pharmacodynamic relationship

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

5.3 Preclinical safety data

Mutagenic and tumourigenic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose BP
Magnesium stearate BP

Capsule shell components

Red iron oxide (E172) HSE
Black iron oxide (E172) HSE
Titanium dioxide (E171) HSE
Gelatin USP

Quinolene Yellow (E104) HSE
Indigotine (E132) HSE
Titanium Dioxide (E171) HSE
Gelatin USP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Plastic bottles – 2 years when stored as recommended.

Blister packs - 2 years when stored as recommended.

6.4 Special precautions for storage

Do not store above 25ºC

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

The product is packed in:

1) Opaque plastic containers composed of polypropylene tubes and polyethylene made tamper-evident closures in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1,000 capsules.

2) Opaque plastic containers composed of either high density polypropylene or high density polyethylene with a tamper-evident or child-resistant tamper-evident closure composed of high density polyethylene in pack sizes of 28, 30, 42, 50, 56, 60, 84, 90, 100, 112, 250, 500 and 1,000 capsules.

3) HDPE container with PP lid & induction seal liner. Pack size of 100 capsules.

4) Blister packs of aluminium / opaque PVC in pack sizes of 28, 30, 42, 56, 60, 84, 90, 100 and 112 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special instructions for handling.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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Sarum Hill, Basingstoke,
RG21 8SR, UK.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0038

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 december 2003
Date of latest renewal: 11 march 2009

10 DATE OF REVISION OF THE TEXT

27/06/2025