SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlordiazepoxide 5mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlordiazepoxide Hydrochloride 5mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule
Size 4 Capsule. Body: yellow, Cap: black.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For short term (2 – 4 weeks only) use

- Symptomatic relief 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.
- Muscle spasm of varied aetiology.
- Symptomatic relief of acute alcohol withdrawal.

Not for use

- Long term (i.e. longer than 4 weeks)
- For mild anxiety
- In children

4.2 Posology and method of administration

Route of administration: oral and must be taken with water and not be chewed.

Prior to starting treatment with chlordiazepoxide, a discussion should be held with patients to put in place a strategy for ending treatment with

chlordiazepoxide in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Posology:
Treatment to be given

- under close medical supervision
- at the lowest effective dose
- for the shortest possible duration (not exceeding 4 weeks)

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.

The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free.

Extension of use should not take place without further clinical evaluation. 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.

Chronic use not recommended (little is known of the long term safety and efficacy: potential for dependence – see section 4.4).

When treatment is started the patient should be informed that

- treatment will be of limited duration
- the dosage will be progressively decreased
- there is the possibility of rebound phenomena.

Anxiety

Adults

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
Adults

- 10-30mg at bed time.
- Treatment would normally vary from a few days to two weeks with a maximum including a tapering-off process of four-weeks.

Muscle Spasm
Adults
10 mg to 30 mg daily in divided doses.

Symptomatic relief of acute alcohol withdrawal
Adults
25 to 100 mg, repeated if necessary in 2hrs to 4hrs.

Special populations

Elderly and/or debilitated patients
Dosage should not exceed half the adult dose.

Children
Chlordiazepoxide Capsules are not for paediatric use.

Patients with organic brain damage, respiratory impairment and/or hepatic or renal dysfunction

- Dosage should not exceed half the adult dose and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide
- Contraindicated in severe hepatic insufficiency (see section 4.3)

Patients who have taken benzodiazepines for a prolonged time may require a longer period of dosage reduction and specialist help may be appropriate.

4.3 Contraindications

- Hypersensitivity to benzodiazepines/active substance chlordiazepoxide or to any of the excipients listed in section 6.1.
- Severe pulmonary insufficiency: respiratory depression: sleep apnoea syndrome (risk of further respiratory depression)
- Phobic and obsessional states (inadequate evidence of safety and efficacy)
- Severe hepatic insufficiency (may precipitate encephalopathy)

- Planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons – see section 4.6)
- Myasthenia gravis
- Chronic psychosis.
- Spinal or cerebral ataxia

  Chlordiazepoxide should not be used alone in depression or anxiety with depression (may precipitate suicide).

4.4 Special warnings and precautions for use

Drug dependence, tolerance and potential for abuse:
Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.
For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.
Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for treatment with chlordiazepoxide should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Tolerance:

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

Dependence:

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. Therefore

- regular monitoring of such patients is essential
- routine repeat prescriptions should be avoided
- treatment should be withdrawn gradually.

Withdrawal effects:

The duration of treatment should be as short as possible (see section 4.2) depending on the indication, but should not exceed 4 weeks, including tapering-off process. If physical dependence has developed, abrupt termination of treatment results in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion, depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea, sleep disturbance and mood changes following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time. In severe cases the following may occur: a feeling of unreality or of being separated from the body (derealisation), depersonalisation, hyperacusis, confusional state, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, psychotic manifestations including hallucinations or epileptic seizures. Withdrawal symptoms will be worse in patients who have been dependent on alcohol or other narcotic drugs in the past, but can occur following abrupt cessation of treatment in patients receiving normal therapeutic doses for a short period of time.

When chlordiazepoxide is being used it is important not to change to a benzodiazepine with a short duration of action, as withdrawal symptoms may be precipitated. 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.

Drug withdrawal syndrome

Prior to starting treatment with chlordiazepoxide, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with chlordiazepoxide should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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 (see section 4.2).

Amnesia:

Anterograde amnesia may occur, most often several hours after ingestion. To reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8).

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 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).

Bereavement/loss:

Psychological adjustment may be inhibited by benzodiazepines

Psychiatric and 'paradoxical' reactions:

Rare behavioural effects such as restlessness, agitation, irritability, aggressiveness, excitement, confusion, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects can occur. These reactions are more likely to occur in children and the elderly, and extreme caution should be used in prescribing benzodiazepines to patients with personality disorders. Should they occur, treatment should be discontinued.

Specific Patient Groups:

Intolerance to sugars

WARNING:

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

Elderly patients

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.

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

Patients with hepatic insufficiency

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.

Patients with depression

Chlordiazepoxide should not be used alone to treat depression or anxiety associated with depression because suicide may be precipitated in such patients.

Patients with a history of alcohol & drug abuse

Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse (risk of abuse/dependence).

Patients with phobias and/or chronic psychoses
Chlordiazepoxide is not recommended (inadequate evidence of efficacy and safety).

Patients with psychotic illness
Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Patients with personality disorders
Extreme caution should be used in prescribing benzodiazepines to patients with personality disorders.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Alcohol: 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.

Sodium oxybate: avoid concomitant use (enhanced effects of sodium oxybate)

Take into account

Centrally acting drugs: Enhancement of the central depressive effect may occur if chlordiazepoxide is combined with centrally acting drugs such as neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates and sedative antihistamines. The elderly may require special supervision.

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

Anti-epileptic drugs: When used concurrently, side effects and toxicity may be more evident, particularly with hydantoins (eg phenytoin) and/or barbiturates or combination including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Narcotic analgesics: Enhancement of the euphoria may also occur leading to increased psychological dependence.
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).

Other drugs enhancing the sedative effect of chlordiazepoxide: cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants baclofen and tizanidine.

Compounds that affect hepatic enzymes (particularly cytochrome P450):

- inhibitors (e.g. Cimetidine, omeprazole, macrolide antibiotics (erythromycin) and disulfiram) have shown to reduce clearance and may potentiate the action of benzodiazepines. The same applies to the use of contraceptive agents
- Known inducers of hepatic enzymes (e.g. rifampicin) may increase clearance of benzodiazepines.

Antihypertensives, vasodilators & diuretics: Enhanced hypotensive effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics. 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

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

Sedative effects are possibly increased when benzodiazepines are given with moxonidine

Dopaminergics: possible antagonism of the effect of levodopa

Effects of benzodiazepines are possibly reduced by theophylline.

4.6 Fertility, Pregnancy and lactation

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 (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 physician 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 breast-feeding.

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 Librium and for 4 months following completion of treatment.

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. Patients should be advised that sedation, amnesia, impaired concentration, dizziness, blurred vision and impaired muscle function may occur and that if affected, they should not drive or use machines, or take part in other activities where this would put themselves or others at risk. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

Concurrent medication may increase these effects (see section 4.5). 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 light-headedness and drowsiness, sedation, unsteadiness and ataxia; these are dose related but even after a single dose, may persist into the following day. 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 central depressant drugs and may experience confusion, especially if organic brain changes are present; the dosage of chlordiazepoxide should not exceed onehalf that recommended for other adults (see section 4.2).

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 reaction, 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)
	Drug dependence (see section 4.4)

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:	
Frequency not known:	Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly. 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 Drug withdrawal symptoms (see 4.4 Special warnings and precautions). Symptoms reported following discontinuation of chlordiazepoxide include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of “rebound” phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed. In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks,

	vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Amnesia
Anterograde amnesia may occur at the therapeutic doses, with increasing risk at higher doses. This may be associated with inappropriate behavior (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 behavior and other adverse behavioural effects are known to occur when using benzodiazepinelike 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.

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.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Management

- Maintain clear airway and adequate ventilation, if indicated
- The benefit of gastric decontaminants is uncertain. Consider activated charcoal (50g for an adult: 1g/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.
- Gastric lavage – unnecessary if only benzodiazepine taken
- Supportive measures as indicated by the patients clinical condition
- 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 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 or as a "diagnostic test".

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeiutic group: Psycholeptics, anxiolytics, benzodiazepine 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 muscle relaxant and anticonvulsant effects.

Chlordiazepoxide has a low affinity as an agonist at specific benzodiazepine receptors, located on GABA-ergic neurones. Stimulation of benzodiazepine receptors potentiates the actions of GABA, which in turn controls the flow of chloride ions across neuronal membranes. An endogenous benzodiazepine has been postulated, but not as yet demonstrated. GABA-ergic neurones are inhibitory in the nervous system. This results in diminuation of some 5-HT, dopamine and noradrenergic neurotransmitter system effects.

5.2 Pharmacokinetic properties

Absorption:

Chlordiazepoxide is completely absorbed after oral administration and peak plasma concentrations are seen between one and two hours after administration.
Steady-state levels are usually reached within three days.

Distribution:

Chlordiazepoxide is metabolised to desmethyl-chlordiazepoxide. Demoxepam and desmethyldiazepam 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 of 6 – 30 hours.

In the elderly the rate of metabolism and excretion of chlordiazepoxide and its active metabolytes is significantly reduced.

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 monohydrate
Maize starch
Sodium starch glycollate (type A)
Magnesium stearate
Titanium dioxide (E171)
Erythrosine (E127)
Quinoline yellow (E104)
Gelatin
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months for polypropylene containers.

24 months for blister packs.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package. Keep blister in the outer carton.

6.5 Nature and contents of container

Cylindrical, polypropylene container with polyethylene tamper-evident cap and polyethylene or polyurethane inserts or blisters composed of PVC/PVdC and aluminium foil.

Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000

Not all packs may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 36722/0101

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