SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Chlordiazepoxide 10 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlordiazepoxide hydrochloride equivalent to 10mg Chlordiazepoxide

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

Plain, biconvex, mid-green, film coated tablets

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 (ie longer than 4 weeks)
- For mild anxiety
- In children

4.2 Posology and method of administration

Route of administration: oral

Treatment to be given

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

Extension of use should not take place without further clinical evaluation

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*
- Starting dose 5 mg daily: usual dose up to 30mg in divided doses increasing to a maximum of 100 mg daily, in divided doses adjusted on an individual basis.
- Treatment should not continue at full dose for more than 2 weeks with a 2 week 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 of four weeks including two weeks tapering off.

**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 Film-coated Tablets are not for paediatric use.

*Patients with impaired hepatic or renal function*
- 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 or to any of the other ingredients
- Acute pulmonary insufficiency: respiratory depression: sleep apnoea syndrome (risk of further respiratory depression)
- 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

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

### 4.4 Special warnings and precautions for use

**Tolerance**
Loss of efficacy to the hypnotic effects may develop after repeated use for a few weeks.

**Dependence**
The risk of dependence (physical or psychological) increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse or in patients with a marked personality disorder. 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)

If physical dependence has developed, abrupt termination of treatment results in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability, sleep disturbance and mood changes. In severe cases the following may occur: a feeling of unreality or of being separated from the body, depersonalisation, 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.

**Rebound symptoms**
Symptoms including insomnia and anxiety may occur on withdrawal of treatment. As this is greater after abrupt discontinuation of treatment, the dose should be 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).

**Bereavement/loss**
Psychological adjustment may be initiated by benzodiazepines.

**Psychiatric and ‘paradoxical’ reactions**
Reactions 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 should not be given to patients with rare hereditary problems of galactose intolerance the Lapp lactase deficiency or glucose-galactose malabsorption.

**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).

### 4.5 Interaction with other medicinal products and other forms of interaction

**Not recommended**

**Alcohol:** Chlordiazepoxide should not be used together with alcohol (enhanced sedative effects: affect the ability to drive or operate machinery).

**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.

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

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

**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) reduce clearance and may potentiate the action of benzodiazepines
- inducers (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.

**Dopaminergics:** possible antagonism of the effect of levodopa

### 4.6 Pregnancy and lactation

**Pregnancy**
Chlordiazepoxide should only be used during pregnancy if there are compelling reasons (e.g. no alternative: benefit outweighs risk).

An increased risk of congenital malformations in humans has been associated with its use, particularly in the first and second trimester. If the product is prescribed to a woman of
childbearing potential, she should be warned to contact her physician regarding stopping if she intends to become pregnant.

If the product is administered at high doses during the late phase of pregnancy or during labour, effects on the neonate, such as hypothermia, irregularities in foetal heart rate, hypotonia, poor-sucking and moderate respiratory depression, can be expected. Infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have physical dependence and may be at some risk of withdrawal symptoms in the postnatal period.

**Lactation**

Use during lactation should be avoided as chlordiazepoxide is found in breast milk.

### 4.7 Effects on ability to drive and use machines

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).

### 4.8 Undesirable effects

#### Common adverse 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. 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 one-half that recommended for other adults (see section 4.2).

Other adverse effects include dependence, confusion, restlessness, agitation, irritability, aggressive outbursts, delusion, nightmares, hallucinations, inappropriate behaviour, tremor, dysarthria, salivation changes, incontinence and thrombocytopenia/other blood disorders. Depression and amnesia can result from high doses (see also below).

Rare adverse effects include numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, blurred vision, hypotension, gastrointestinal upsets, skin rashes, visual disturbances, changes in libido, and urinary retention.

Isolated cases of blood dyscrasias and jaundice have also been reported.

#### Amnesia

Anterograde amnesia may occur at therapeutic dosages, 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 benzodiazepine.

#### 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 benzodiazepines or 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 (see
warnings and precautions). Psychological dependence may occur. Abuse of benzodiazepines has been reported (see sections 4.2 & 4.4).

4.9 Overdose

Benzodiazepines potentiate the effects of other CNS depressants including alcohol.

Features

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Coma, hypotension and respiratory depression, occasionally occur but are seldom serious if these drugs are taken alone. Coma usually lasts a few hours but in the elderly may be more protracted and cyclical. Respiratory depression is more serious in those with severe obstructive airways disease. Patients who are asymptomatic at 4 hours are unlikely to develop symptoms.

Management

- Maintain clear airway and adequate ventilation, if indicated
- The value of gastric decontaminants is uncertain. Consider activated charcoal (50g for an adult: 1g/Kg for a child) within 1 hour of ingestion if more than 1mg/Kg has been taken provided the patient is not too drowsy.
- Gastric lavage – unnecessary if only benzodiazepine is taken
- Supportive measures as indicated by the patients clinical condition
- Rarely flumazenil may be used as an antidote, however it has a short half-life (about 1 hour). It should not be used in mixed overdoses or as a “diagnostic test”.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Chlordiazepoxide acts as an agonist at specific benzodiazepine receptors, located as membranes of GABA-ergic neurones. Benzodiazepine and GABA receptors form complexes with chloride ion channels. 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

Chlordiazepoxide is completely absorbed after oral administration and peak plasma concentrations are seen between one and two hours. The systemic bio-availability of an oral dose is close to 100% with peak blood levels being reached between 1 – 2 hours after administration. The mean plasma half-life is about 15 hours with a range of 5-30 hours. Chlordiazepoxide is converted to active metabolites such as desmethyl chlordiazepoxide, with a mean half-life of 16 hours, demoxepam with a mean half-life of 45 hours and desmethyldiazepam with a half-life of approximately 50 hours as well as oxazepam and nordiazepam, all of these have long half-lives, they tend to accumulate in the body and exert a significant pharmacological activity during chronic administration.

Chlordiazepoxide has an apparent volume of distribution of between 0.22 l.kg-1 and 0.75 l.kg-1. Highest levels of the drug are found in the lipid-rich areas such as the brain and adipose tissue. Chlordiazepoxide also accumulates in reticulocytes, muscle, kidney and the
myocardium, and are found there in higher concentrations than in the plasma. The plasma protein binding is 92-96%. Liver disease reduces the proportion of protein binding thus increasing the free drug concentration. Protein binding is also significantly reduced in chronic renal failure.

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

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Maize starch
Magnesium stearate
Lactose monohydrate
Pregelatinised maize starch

Film coating:
Hypermellose
Ethylcellulose
Diethylphthalate
Brilliant Blue (E133)
Indigo Carmine (E132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months for cylindrical polypropylene containers
24 months for blister packs.

6.4 Special precautions for storage

Do not store above 25º C. 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 PVC/PVdC/Al blister packs
Pack sizes: 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000
Not all packs may be marketed

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 instructions

7. MARKETING AUTHORISATION HOLDER
8.  MARKETING AUTHORISATION NUMBER(S)

PL 08553/0071

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/06/2006

10.  DATE OF REVISION OF THE TEXT

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