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PL 08553/0070
CHLORDIAZEPoxide 10mg Film-Coated Tablets
PL 08553/0071
CHLORDIAZEPoxide 10mg Capsules
PL 08553/0110
CHLORDIAZEPoxide 5mg Capsules
PL 08553/0111

LAY SUMMARY

The MHRA granted Dr Reddy’s Laboratories (UK) Limited Marketing Authorisations (licences) for the medicinal product Chlordiazepoxide 5mg and 10mg Film-Coated Tablets (PL 08553/0070-71) and Chlordiazepoxide 10mg and 5mg Capsules (PL 08553/0110-111) on 1st June 2006. These prescription-only medicines are for the short-term relief of anxiety that is severe and disabling, or subjecting the individual to unacceptable distress, muscle spasm, and relief of acute alcohol withdrawal.

Chlordiazepoxide 5mg and 10mg Film-Coated Tablets and Chlordiazepoxide 10mg and 5mg Capsules contain the active ingredient chlordiazepoxide hydrochloride which acts as an anti-anxiety, sedative, appetite stimulant and weak pain relief.

These applications were submitted as abridged simple applications of previously granted applications, Tropium Tablets 5mg and Tropium Tablets 10mg (PL 00225/5098R and 5099R), and Chlordiazepoxide Capsules 5mg and 10mg Tropium (PL 00225/5075R and 5076R), which were initially granted licences in June 1983.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Chlordiazepoxide 5mg and 10mg Film-Coated Tablets and Chlordiazepoxide 10mg and 5mg Capsules outweigh the risks, hence, Marketing Authorisations have been granted.
SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Chlordiazepoxide 5mg and 10mg Film-Coated Tablets (PL 08553/0070-71) and Chlordiazepoxide 10mg and 5mg Capsules (PL 08553/0110-111) to Dr Reddy’s Laboratories (UK) Limited on 1st June 2006. The products are prescription-only medicines (POM).

The applications were submitted as simple abridged applications according to Article 10c (formerly 10.1(a)(i)) of Directive 2001/83/EC, as amended, cross-referring to Tropium Tablets 5mg and Tropium Tablets 10mg (PL 00225/5098R and 5099R), and Chlordiazepoxide Capsules 5mg and 10mg Tropium (PL 00225/5075 and 5076R), which were initially granted licences in 1983.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference product. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated for them.

The products contain the active ingredient chlordiazepoxide hydrochloride which acts as an anti-anxiety, sedative, appetite stimulant and weak analgesic. Chlordiazepoxide 5mg and 10mg Film-Coated Tablets (PL 08553/0070-71) and Chlordiazepoxide 10mg and 5mg Capsules (PL 08553/0110-111) are indicated for the short-term relief of anxiety that is severe and disabling, or subjecting the individual to unacceptable distress, muscle spasm, and relief of acute alcohol withdrawal.
1. INTRODUCTION
These are simple, piggy back applications for Chlordiazepoxide 5mg and 10mg Film-Coated Tablets, and Chlordiazepoxide 10mg and 5mg Capsules submitted under Article 10c (formerly 10.1(a)(i)) of Directive 2001/83/EC, as amended. The proposed MA holder is Dr Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK.

These applications cross refer to standard abridged applications for Tropium Tablets 5mg and Tropium Tablets 10mg (PL 00225/5098R and 5099R), and Chlordiazepoxide Capsules 5mg and 10mg Tropium (PL 00225/5075R and 5076R), which are currently registered in the UK. These applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name(s)
The proposed names of the products are Chlordiazepoxide 5mg and 10mg Film-Coated Tablets, and Chlordiazepoxide 10mg and 5mg Capsules. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The film-coated tablets contain either 5mg or 10mg chlorodiazepoxide as the HCl salt. The capsules contain 5mg or 10mg chlorodiazepoxide hydrochloride. They are to be stored in either polypropylene containers with polyethylene lids or aluminium/PVDC/PVC blisters with cardboard outer cartons.

For product packaged in either packaging, the pack sizes are 28, 30, 50, 56, 60, 84, 100, 250, 500 and 1000 film-coated tablets/capsules.

The proposed shelf-life of 36 months for the polypropylene containers and 24 months for the blister packs is consistent with the cross-reference products. The storage conditions for the blister packs are “Do not store above 25°C. Store in original package. Keep blister in the outer carton” and for the polypropylene/polyethylene containers are “Do not store above 25°C. Store in original package”.

2.3 Legal status
On approval, the products will be subject to medical prescription by healthcare professionals only (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Dr Reddy’s Laboratories (UK) Ltd, 6 Riverview Road, Beverley, East Yorkshire, HU17 0LD, UK.

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference products.

2.9 Finished product specification
The proposed finished product specification for each product is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The only material of animal/human origin is lactose monohydrate. This source is exempt from the need for control in accordance with a public statement issued from the BWP. No other materials of animal or human origin are included in the product.

3. EXPERT REPORTS
The applicant has included detailed expert reports in Module 2 of the application. Signed declarations and copies of the experts’ CVs are enclosed in Module 1.4 for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/CARTON
A satisfactory patient information leaflet has been prepared.

Carton and blister
The proposed artwork complies with statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with the applications are acceptable. Marketing Authorisations should be granted.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

As these are duplicate applications to Tropium Tablets 5mg and Tropium Tablets 10mg (PL 00225/5098R and 5099R), and Chlordiazepoxide Capsules 10mg and 5mg Tropium (PL 00225/5075R and 5076R), no new clinical data have been supplied and none are required.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such has been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Chlordiazepoxide hydrochloride is a well known drug and has been used for the proposed indications for many years. These applications are identical to previously granted applications for Tropium Tablets 5mg and Tropium Tablets 10mg (PL 00225/5098R and 5099R), and Chlordiazepoxide Capsules 10mg and 5mg Tropium (PL 00225/5075R and 5076R).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with chlordiazepoxide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
CHLORDIAZEPOXIDE 5MG FILM-COATED TABLETS
PL 08553/0070

CHLORDIAZEPOXIDE 10MG FILM-COATED TABLETS
PL 08553/0071

CHLORDIAZEPOXIDE 10MG CAPSULES
PL 08553/0110

CHLORDIAZEPOXIDE 5MG CAPSULES
PL 08553/0111

STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 21/05/2003.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 09/07/2003.</td>
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<td>Following assessment of the application the MHRA requested further information on 02/09/2003 and 03/02/2006.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 09/05/2005 and 16/03/2006</td>
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<td>5</td>
<td>The application was determined on 02/06/2006</td>
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**CHLORDIAZEPoxide 5mg Film-Coated Tablets**  
PL 08553/0070  
**CHLORDIAZEPoxide 10mg Film-Coated Tablets**  
PL 08553/0071  
**CHLORDIAZEPoxide 10mg Capsules**  
PL 08553/0110  
**CHLORDIAZEPoxide 5mg Capsules**  
PL 08553/0111

**Steps Taken After Assessment**

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CHLORDIAZEPoxide 5mg Film-coated Tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Chlordiazepoxide 5 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Chlordiazepoxide hydrochloride equivalent to 5mg 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
The short-term relief (2-4 weeks only) 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.

4.2. Posology and method of administration
Route of administration: oral
Not recommended for use in children.

When treatment is started it may be useful to inform the patient that treatment 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 has been discontinued.

Anxiety
The starting dose should be 5 mg daily increasing to a maximum of 100 mg daily, in divided doses adjusted on an individual basis. Treatment should always be as short as possible and should not normally exceed 8-12 weeks including tapering off process. Extension should not take place without re-evaluation of the situation.

In the elderly and debilitated patients the dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Insomnia associated with anxiety
In adults, the dose should be 10-30mg at bed time. Treatment should be as short as possible and would normally vary from a few days to two weeks with a maximum, including tapering off of four weeks. Where extension beyond the maximum treatment period may be necessary it should not take place without re-evaluation of the patients status.

In the Elderly and debilitated patients dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Muscle Spasm
10 mg to 30 mg daily in divided doses.
Symptomatic relief of acute alcohol withdrawal
25 to 100 mg, repeated if necessary in 2hrs to 4hrs.

4.3. Contraindications
- Myasthenia gravis
- Hypersensitivity to benzodiazepines or to any of the other ingredients.
- Acute pulmonary insufficiency
- Respiratory depression
- Sleep apnoea syndrome
- Severe hepatic insufficiency

4.4. Special warnings and precautions for use

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

Dependence
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. Dependence may be physical or psychological. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. 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 or epileptic seizures.

Rebound insomnia and anxiety: 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 and should not exceed four weeks for insomnia and 8-12 weeks in case of anxiety, including tapering off process. 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. Patients should be made aware of the possibility of rebound phenomena, thereby minimising anxiety other such symptoms should they occur while the product is being discontinued. When chlordiazepoxide is being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia
Chlordiazepoxide 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.

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. Should this occur, treatment with the product should be discontinued. They are more likely to occur in children and the elderly.

Specific Patient Groups
WARNING: Chlordiazepoxide should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Chlordiazepoxide is not recommended for the primary treatment of psychotic illness.

Chlordiazepoxide should not be used alone to treat depression or anxiety associated with depression because suicide may be precipitated in such patients.
Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse.

Not for use in phobic or obsessional states (inadequate evidence of efficacy and safety).

Chlordiazepoxide should not be given to children without careful assessment, and the duration of treatment must be kept to a minimum. The elderly should be given a reduced dose (see Posology). 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.

4.5. Interaction with other medicinal products and other forms of interaction
Chlordiazepoxide should not be used together with alcohol as this may enhance the sedative effects and affect the ability to drive or operate machinery.

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

When chlordiazepoxide 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.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Drugs which enhance the sedative effect of chlordiazepoxide are: cisapride, lofexidine, nabilone, and the muscle-relaxants baclofen and tizanidine. Cimetidine inhibits the metabolism of chlordiazepoxide resulting in increased plasma concentration.

4.6. Pregnancy and lactation
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

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.

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

4.7. Effects on ability to drive and use machines
Sedation, amnesia, impaired concentration and impaired muscle 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 Interactions).

4.8. Undesirable effects
Common adverse effects include drowsiness, sedation, unsteadiness and ataxia; these are dose related and may persist into the following day even after a single dose. 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.

Other adverse effects are rare and include numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, 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 using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (See warnings and precautions).

**Depression**
Pre-existing depression may be unmasked during benzodiazepine use.

**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.

4.9. **Overdose**
Symptoms: varying degrees of CNS depression, ranging from drowsiness to coma. Symptoms in mild cases 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: vomiting, should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Flumazenil may be useful as an antidote.

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%. 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 desmethyl Diazepam 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 reticuloocytes, 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,
Patent Blue V (E131)
Indigotine (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 in the outer container.

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
Dr. Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8. MARKETING AUTHORISATION NUMBER
PL 08553/0070

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/06/2006

10 DATE OF REVISION OF THE TEXT
01/06/2006
CHLORDIAZEPoxide 10mg Film-Coated Tablets

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
The short-term relief (2-4 weeks only) 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.

4.2. Posology and method of administration
Route of administration: oral
Not recommended in children

When treatment is started it may be useful to inform the patient that treatment 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 has been discontinued.

Anxiety
The starting dose should be 5 mg daily increasing to a maximum of 100 mg daily, in divided doses adjusted on an individual basis. Treatment should always be as short as possible and should not normally exceed 8-12 weeks including tapering off process. Extension should not take place without re-evaluation of the situation.

In the elderly and debilitated patients the dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Insomnia associated with anxiety
10-30mg at bed time. Treatment should be as short as possible and would normally vary from a few days to two weeks with a maximum, including tapering off of four weeks. Where extension beyond the maximum treatment period may be necessary it should not take place without re-evaluation of the patients status.

In the Elderly and debilitated patients dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Muscle Spasm
10 mg to 30 mg daily in divided doses.
Symptomatic relief of acute alcohol withdrawal
25 to 100 mg, repeated if necessary in 2hrs to 4hrs.

4.3. Contraindications
Myasthenia gravis
Known hypersensitivity to benzodiazepines or to any of the other ingredients
Acute pulmonary insufficiency
Respiratory depression
Sleep apnoea syndrome
Severe hepatic insufficiency

4.4. Special warnings and precautions for use

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

Dependence
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. Dependence may be physical or psychological. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypsersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound insomnia and anxiety: 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 and should not exceed four weeks for insomnia and 8-12 weeks in case of anxiety, including tapering off process. 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. Patients should be made aware of the possibility of rebound phenomena, thereby minimising anxiety other such symptoms should they occur while the product is being discontinued. When chlordiazepoxide is being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia
Chlordiazepoxide 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.

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. Should this occur, treatment with the product should be discontinued. They are more likely to occur in children and the elderly.

Specific Patient Groups
WARNING: Chlordiazepoxide should not be given to patients with rare hereditary problems of galactose intolerance the Lapp lactase deficiency pr glucose-galactose malabsorption.

Chlordiazepoxide is not recommended for the primary treatment of psychotic illness.

Chlordiazepoxide should not be used alone to treat depression or anxiety associated with depression because suicide may be precipitated in such patients.
Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse.

Not for use in phobic or obsessional states (inadequate evidence of efficacy and safety).

Chlordiazepoxide should not be given to children without careful assessment, and the duration of treatment must be kept to a minimum. The elderly should be given a reduced dose (see Posology). 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.

4.5. Interaction with other medicinal products and other forms of interaction
Chlordiazepoxide should not be used together with alcohol as this may enhance the sedative effects and affect the ability to drive or operate machinery.

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

When chlordiazepoxide 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.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Drugs which enhance the sedative effect of chlordiazepoxide are: cisapride, lofexidine, nabilone, and the muscle-relaxants baclofen and tizanidine. Cimetidine inhibits the metabolism of chlordiazepoxide resulting in increased plasma concentration.

4.6. Pregnancy and lactation
If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

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.

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

4.7. Effects on ability to drive and use machines
Sedation, amnesia, impaired concentration and impaired muscle 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 Interactions).

4.8. Undesirable effects
Common adverse effects include drowsiness, sedation, unsteadiness and ataxia; these are dose related and may persist into the following day even after a single dose. 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.

Other adverse effects are rare and include numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, hypotension, gastrointestinal upsets, skin rashes, visual disturbances, changes in libido, and urinary retention. Isolated cases of blood dyscrasias and jaundice have also been reported.

**Ammnesia**
Ammensurate amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (See warnings and precautions).

**Depression**
Pre-existing depression may be unmasked during benzodiazepine use.

**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.

**4.9. Overdose**
Symptoms: varying degrees of CNS depression, ranging from drowsiness to coma. Symptoms in mild cases 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: vomiting, should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Flumazenil may be useful as an antidote.

**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%. 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
Patent Blue V (E131)
Indigotine (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
Dr. Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8. MARKETING AUTHORISATION NUMBER
PL 08553/0071

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/06/2006

10. DATE OF REVISION OF THE TEXT
01/06/2006
CHLORDIAZEPoxide 10mg Capsules
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Chlordiazepoxide 10mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Chlordiazepoxide Hydrochloride 10 mg
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Capsule

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
The short-term relief (2-4 weeks only) 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.

The use of benzodiazepines to treat short-term ‘mild’ anxiety is considered to be inappropriate and unsuitable.

Muscle spasm of varied aetiology.

Symptomatic relief of acute alcohol withdrawal.

Not recommended for use in children.

4.2. Posology and method of administration
Route of administration: oral

When treatment is started it may be useful to inform the patient that treatment 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 has been discontinued.

Anxiety
In adults, the starting dose should be 5 mg daily increasing to a maximum of 100 mg daily, in divided doses adjusted on an individual basis. Treatment should always be as short as possible and should not normally exceed 8-12 weeks including tapering off process. Extension should not take place without re-evaluation of the situation.

In elderly and debilitated patients, dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Insomnia associated with anxiety
In adults, the dose should be 10-30 mg at bed time. Treatment should be as short as possible and would normally vary from a few days to two weeks with a maximum, including tapering off of four weeks. Where extension beyond the maximum treatment period may be necessary it should not take place without re-evaluation of the patients status.

In elderly and debilitated patients, the dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.
**Muscle Spasm**
In adults, the dose should be 10 mg to 30 mg daily in divided doses.

**Symptomatic relief of acute alcohol withdrawal**
In adults, the dose should be 25 to 100 mg, repeated if necessary in 2hrs to 4hrs.

### 4.3. Contraindications
- Myasthenia gravis
- Hypersensitivity to benzodiazepines or to any of the other ingredients
- Acute pulmonary insufficiency
- Respiratory depression
- Sleep apnoea syndrome
- Severe hepatic insufficiency

### 4.4. Special warnings and precautions for use

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

#### Dependence
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. Dependence may be physical or psychological.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. 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 or epileptic seizures.

Rebound insomnia and anxiety: 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 Posology) and should not exceed four weeks for insomnia and 8-12 weeks in case of anxiety, including tapering off process. 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. Patients should be made aware of the possibility of rebound phenomena; thereby minimising anxiety other symptoms should they occur while the product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest with the dosage interval, especially when the dosage is high.

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

#### Amnesia
Chlordiazepoxide 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 also Undesirable Effects).

#### Psychiatric and ‘paradoxical’ reactions
Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioral effects are known to...
occur when using benzodiazepines. Should this occur, treatment with the product should be discontinued.

They are more likely to occur in children and the elderly.

**Specific Patient Groups**

**WARNING:** Chlordiazepoxide should not be given to patients with rare hereditary problems of galactose intolerance, the LAPP lactose deficiency or glucose-galactose malabsorption.

Chlordiazepoxide is not recommended for the primary treatment of psychotic illness.

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

Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse.

Not for use in phobic or obsessional states (inadequate evidence of efficacy and safety)

Chlordiazepoxide should not be given to children without careful assessment, and the duration of treatment must be kept to a minimum. The elderly should be given a reduced dose (see Posology). 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.

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

**Not recommended:** Concomitant intake with alcohol

Chlordiazepoxide should not be used together with alcohol as this may enhance the sedative effects and affect the ability to drive or operate machinery.

**Take into account:** Combination with CNS depressants

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

When chlordiazepoxide 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.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Drugs which enhance the sedative effect of chlordiazepoxide are: cisapride, lofexidine, nabilone, and the muscle-relaxants baclofen and tizanidine. Cimetidine inhibits the metabolism of chlordiazepoxide resulting in increased plasma concentration.

### 4.6. Pregnancy and lactation

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.
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.

Since benzodiazepines are found in breast milk, benzodiazepines should not be given to breastfeeding mothers.

4.7. Effects on ability to drive and use machines
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 Interactions).

4.8. Undesirable effects
Common adverse effects include drowsiness, sedation, unsteadiness and ataxia; these are dose related and may persist into the following day even after a single dose. 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.

Other adverse effects are rare and include numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, 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 using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (See warnings and precautions).

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

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.

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

Following overdose with oral benzodiazepines, vomiting, should be induced (within one hour) if the patient is conscious or gastric lavage is undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

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

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES
5.1. **Pharmacodynamic properties**
Chlordiazepoxide acts as an anxiolytic, sedative and hypnotic depending on the dose. It also has a muscle relaxant function in cases of muscular spasticity and is an anti-convulsant.

5.2. **Pharmacokinetic properties**
- Oral absorption: greater than 95%
- Pre-systemic metabolism: less than 5%
- Plasma half-life: 15 hours
- Volume of distribution: 0.22-0.75 l/kg
- Plasma protein binding: 92-96%

Chlordiazepoxide is metabolized by demethylation and hydroxylation to active metabolites.

5.3. **Preclinical safety data**
Not applicable

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**
- Lactose monohydrate
- Maize starch
- Sodium starch glycollate (type A)
- Magnesium stearate
- Titanium dioxide (E171)
- Gelatin
- Quinoline yellow (E104)
- Indigotine (E132)

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 25°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 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 of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.**
No special instructions

7. **MARKETING AUTHORITYHOLD ER**
Dr. Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8. **MARKETING AUTHORIZATION NUMBER**
PL 08553/0110

9. **DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION**
01/06/2006

10. **DATE OF REVISION OF THE TEXT**
1. NAME OF THE MEDICINAL PRODUCT
Chlordiazepoxide 5mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Chlordiazepoxide Hydrochloride 5 mg
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Capsule

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
The short-term relief (2-4 weeks only) 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.

The use of benzodiazepines to treat short-term ‘mild’ anxiety is considered to be inappropriate and unsuitable.

Muscle spasm of varied aetiology.

Symptomatic relief of acute alcohol withdrawal.

Not recommended for use in children.

4.2. Posology and method of administration
Route of administration: oral
When treatment is started it may be useful to inform the patient that treatment 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 has been discontinued.

Anxiety
In adults, the starting dose should be 5 mg daily increasing to a maximum of 100 mg daily, in divided doses adjusted on an individual basis. Treatment should always be as short as possible and should not normally exceed 8-12 weeks including tapering off process. Extension should not take place without re-evaluation of the situation.

In elderly and debilitated patients, dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.

Insomnia associated with anxiety
In adults, the dose should be 10-30 mg at bed time. Treatment should be as short as possible and would normally vary from a few days to two weeks with a maximum, including tapering off of four weeks. Where extension beyond the maximum treatment period may be necessary it should not take place without re-evaluation of the patients status.

In elderly and debilitated patients, the dosage should not exceed half the adult dose. The same applies to patients with impaired liver or renal function and steps should be taken to ensure that there is no accumulation of plasma chlordiazepoxide in these patients.
**Muscle Spasm**
In adults, the dose should be 10 mg to 30 mg daily in divided doses.

**Symptomatic relief of acute alcohol withdrawal**
In adults, the dose should be 25 to 100 mg, repeated if necessary in 2hrs to 4hrs.

### 4.3. Contraindications
- Myasthenia gravis
- Hypersensitivity to benzodiazepines or to any of the other ingredients.
- Acute pulmonary insufficiency
- Respiratory depression
- Sleep apnoea syndrome
- Severe hepatic insufficiency

### 4.4. Special warnings and precautions for use

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

**Dependence**
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. Dependence may be physical or psychological.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. 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 or epileptic seizures.

Rebound insomnia and anxiety: 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 Posology) and should not exceed four weeks for insomnia and 8-12 weeks in case of anxiety, including tapering off process. 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. Patients should be made aware of the possibility of rebound phenomena; thereby minimising anxiety other symptoms should they occur while the product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest with the dosage interval, especially when the dosage is high.

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

**Amnesia**
Chlordiazepoxide 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 also Undesirable Effects).

**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. Should this occur, treatment with the product should be discontinued.

They are more likely to occur in children and the elderly.

**Specific Patient Groups**

**WARNING:** Chlordiazepoxide should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Chlordiazepoxide is not recommended for the primary treatment of psychotic illness.

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

Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse.

Not for use in phobic or obsessional states (inadequate evidence of efficacy and safety).

Chlordiazepoxide should not be given to children without careful assessment, and the duration of treatment must be kept to a minimum. The elderly should be given a reduced dose (see Posology). 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.

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

**Not recommended:** Concomitant intake with alcohol

Chlordiazepoxide should not be used together with alcohol as this may enhance the sedative effects and affect the ability to drive or operate machinery.

**Take into account:** Combination with CNS depressants

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

When chlordiazepoxide 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.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

Compounds that inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Drugs which enhance the sedative effect of chlordiazepoxide are: cisapride, lofexidine, nabilone, and the muscle-relaxants baclofen and tizanidine. Cimetidine inhibits the metabolism of chlordiazepoxide resulting in increased plasma concentration.

4.6. Pregnancy and lactation

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.
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.

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

4.7. Effects on ability to drive and use machines
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 Interactions).

4.8. Undesirable effects
Common adverse effects include drowsiness, sedation, unsteadiness and ataxia; these are dose related and may persist into the following day even after a single dose. 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.

Other adverse effects are rare and include numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, 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 using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. (See warnings and precautions).

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

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.

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

Following overdose with oral benzodiazepines, vomiting, should be induced (within one hour) if the patient is conscious or gastric lavage is undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

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

Flumazenil may be useful as an antidote.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Chlordiazepoxide acts as an anxiolytic, sedative and hypnotic depending on the dose. It also has a muscle relaxant function in cases of muscular spasticity and is an anti-convulsant.

5.2. Pharmacokinetic properties
Oral absorption greater than 95%
Pre-systemic metabolism less than 5%
Plasma half-life 15 hours
Volume of distribution 0.22-0.75 l.kg
Plasma protein binding 92-96%

Chlordiazepoxide is metabolized by demethylation and hydroxylation to active metabolites.

5.3. Preclinical safety data
Not applicable

6. PHARMAEUTICAL PARTICULARS
6.1. List of excipients
Lactose monohydrate
Maize starch
Sodium starch glycolate (type A)
Magnesium stearate
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 25°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 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 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
Dr. Reddy’s Laboratories (UK) Ltd
6 Riverview Road
Beverley
HU17 0LD
UK

8. MARKETING AUTHORISATION NUMBER
PL 08553/0111

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/06/2006
DATE OF REVISION OF THE TEXT
01/06/2006
CHLORDIAZEPoxide 5mg Film-Coated Tablets
PL 08553/0070
CHLORDIAZEPoxide 10mg Film-Coated Tablets
PL 08553/0071

PRODUCT INFORMATION LEAFLET

Please read this leaflet carefully before you start taking this medicine. Keep this leaflet with the medicine. Read these instructions before you start taking the medicine and repeat the instructions every time you receive a new supply of the medicine. If you have any questions or comments, contact your doctor or pharmacist.

Before you start taking this medicine, consult your doctor or pharmacist. It is very important that you read the product information leaflet before you start taking this medicine. The product information leaflet contains important information about your medicine.

The active ingredient in CHLORDIAZEPoxide 5mg Film-Coated Tablets is CHLORDIAZEPoxide. The recommended dose is 1 tablet. The tablets contain the following excipients: microcrystalline cellulose, magnesium stearate, silicon dioxide, talc, yellow iron oxide, titanium dioxide. The tablets are available in strips of 10 tablets, each containing 5mg of CHLORDIAZEPoxide. The tablets are supplied in blisters. The tablets are supplied in an amber plastic bottle.

If you have any unexplained side effects that concern you, contact your doctor.

Before you start taking this medicine, consult your doctor or pharmacist. It is very important that you read the product information leaflet before you start taking this medicine. The product information leaflet contains important information about your medicine.

The active ingredient in CHLORDIAZEPoxide 10mg Film-Coated Tablets is CHLORDIAZEPoxide. The recommended dose is 1 tablet. The tablets contain the following excipients: microcrystalline cellulose, magnesium stearate, silicon dioxide, talc, yellow iron oxide, titanium dioxide. The tablets are available in strips of 10 tablets, each containing 10mg of CHLORDIAZEPoxide. The tablets are supplied in blisters. The tablets are supplied in an amber plastic bottle.

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Before you start taking this medicine, consult your doctor or pharmacist. It is very important that you read the product information leaflet before you start taking this medicine. The product information leaflet contains important information about your medicine.

The active ingredient in CHLORDIAZEPoxide 5mg and 10mg Film-Coated Tablets is CHLORDIAZEPoxide. The recommended dose is 1 tablet. The tablets contain the following excipients: microcrystalline cellulose, magnesium stearate, silicon dioxide, talc, yellow iron oxide, titanium dioxide. The tablets are available in strips of 10 tablets, each containing 5mg or 10mg of CHLORDIAZEPoxide. The tablets are supplied in blisters. The tablets are supplied in an amber plastic bottle.

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If you have any unexplained side effects that concern you, contact your doctor.
CHLORDIAZEPoxide 10mg Capsules
PL 08553/0110
CHLORDIAZEPoxide 5mg Capsules
PL 08553/0111

PRODUCT INFORMATION LEAFLET

PLEASE READ THIS LEAFLET CAREFULLY BEFORE YOU START TAKING THIS MEDICINE. KEEP THIS LEAFLET. IF YOU HAVE ANY QUESTIONS CONCERNING YOUR MEDICATION, SEE YOUR DOCTOR OR PHARMACIST FOR MORE INFORMATION.

What you need to know about your capsules

The active ingredient of CHLORDIAZEPoxide Capsules is chlordiazepoxide hydrochloride. It belongs to a group of drugs known as benzodiazepines and has tranquilizing properties.

CHLORDIAZEPoxide 5mg capsules contain 5mg chlordiazepoxide hydrochloride. The capsules are yellow and black. They also contain citric monohydrate, maize starch, sodium starch glycolate (type A), magnesium stearate, yellow PEG 400, titanium dioxide, gelatin, and indigo blue.

CHLORDIAZEPoxide 10mg capsules contain 10mg chlordiazepoxide hydrochloride. The capsules are green and white. They also contain citric monohydrate, maize starch, sodium starch glycolate (type A), magnesium stearate, yellow PEG 400, titanium dioxide, gelatin, and indigo blue.

The capsules are available in containers of blister packs of 28, 50, 90, 40, 100, 200, 500, and 1000.

Marketing Authorization holder and manufacturer:

Dr. Reddy’s Laboratories Ltd., India
6 Sherborne Road
Belfast
BT7 1SD
UK

Why have you been prescribed CHLORDIAZEPoxide?

CHLORDIAZEPoxide is used for the treatment of anxiety or distressing anxiety, sleep, or related with sleeping problems; muscle spasm of varied aetiology and symptomatic relief of acute alcoholic withdrawal.

Before taking your medicine

Before taking this medicine, tell your doctor or a qualified health professional if you:

- Have had any allergy or reaction to any of the other ingredients contained in this medicine.
- You have experienced unusual or allergic reactions to this medicine.
- You are pregnant (please consult your doctor/health professional).
- You are breast-feeding.
- You have a history of depression.
- You have had previous suicide.
- You have had a family history of suicide.
- You have a disorder known as myasthenia gravis characterized by muscle weakness sometimes leading to difficulty breathing.
- You have a condition called sleep apnoea where you have difficulty breathing while asleep.

Taking other medicines

Some medicines will affect the actions of CHLORDIAZEPoxide, e.g. neurepinephrine, transmitters, antidepressants, benzodiazepines, and anaesthetics and sedatives as antihistamines, all of which will increase the sedative effects of CHLORDIAZEPoxide. Alcohol will also increase the effects of CHLORDIAZEPoxide by depressing the central nervous system, and should therefore be avoided. Barbiturates and anti-epileptic drugs will increase the sedative effects of CHLORDIAZEPoxide.

Ask your doctor or pharmacist if you are taking the following drugs:

- Drugs that are reductase inhibitors
- Lithium
- Valproate
- Disopyramide
- Thiazides
- Diuretics

If you have a history of alcohol or drug abuse you must tell your doctor before taking this medicine.

If you go to a doctor, dentist or hospital for an operation, tell them you are taking CHLORDIAZEPoxide.

Driving and operating machinery

Your ability to perform skilled tasks may be affected when taking CHLORDIAZEPoxide, especially after altering the doses you are taking. If you feel dizzy or get a tight chest do not attempt to drive or operate dangerous machinery. Alcohol is likely to increase the drowsiness and sedation caused by this medicine, and should not be taken with this medicine.

Pregnancy and breast-feeding

Do not take this medicine if you are pregnant, might become pregnant, or are breast-feeding. If your doctor has decided that you should continue taking CHLORDIAZEPoxide during your pregnancy, it is possible that CHLORDIAZEPoxide may enter your baby's body. Breast-feeding women should not breast-feed if they are taking CHLORDIAZEPoxide.

If you are pregnant or breast-feeding, you should only take CHLORDIAZEPoxide under medical supervision. Complexal (chlormazine) is found in breast milk, it should not be used while breast-feeding.

Taking your medicine

This medicine is to be used by mouth and only in the doses prescribed by your doctor. Do not take more than the dose you are prescribed. Do not stop taking your medicine or change the dose unless your doctor tells you to do so. Do not take alcohol while taking this medicine. You will be prescribed the lowest dose necessary to control your symptoms for a limited period only. Thereafter there will be a tapering of period, which requires that the dosage will be progressively reduced.

CHLORDIAZEPoxide is not recommended for use in children.

Designs:

Aznis:

- A big daily dose (10 to 100mg) is necessary to treat severe anxiety or depression.
- Long-term treatment is not recommended.

Dolina and dilated pupils:

- Halves adult dose

Incontinence associated with anxiety:

Aznis:

- 10 to 20mg before going to bed. Treatment will be as short as possible and will normally last from 1 to 2 weeks with a maximum, including the tapering-off period, of 4 weeks. Where remission beyond the maximum treatment period is necessary this will only take place after re-evaluation of the condition by the patient's doctor.

Dolina and dilated pupils:

- Halves adult dose

Main effects:

Aznis:

- 10mg to 20mg daily or divided doses.

Symptoms of acute alcohol withdrawal:

- Adults: 25 to 100mg, repeated if necessary or 3 to 5 times in 24 hours.

Cautions:

If you think you are taking too much of this medicine, please contact your doctor or pharmacist immediately. Do not take any more of this medicine and do not take any other medicine for the same problem unless your doctor or pharmacist tells you to.

If you think you have taken too much of this medicine, please contact your doctor or pharmacist immediately.

If you are pregnant or breast-feeding, you should only take CHLORDIAZEPoxide under medical supervision.

If you have any concerns or are not sure about anything, ask your doctor or pharmacist who have access to this additional information.

Date of preparation: 08.02.94
Chlordiazepoxide Capsules, PL 08553/0110
Chlordiazepoxide Film-Coated Capsules, PL 08553/0111
6 Dr. Reddy's Laboratories (UK) Ltd.

Component code M78480
CHLORDIAZEPOXIDE 5MG FILM-COATED TABLETS
PL 08553/0111

LABELLING

Each capsule contains chlordiazepoxide hydrochloride 5mg. Also contains lactose monohydrate.

Capsule for oral use. Use as directed by the physician. Please read the enclosed leaflet before use. Do not store above 25°C. Store in the original package. Keep out of the reach and sight of children.

MHRA PAR – Chlordiazepoxide 5mg and 10mg Film-Coated Tablets  - 37 -
Each capsule contains chlordiazepoxide hydrochloride 5mg. Also contains lactose monohydrate. Capsule for oral use. Use as directed by the physician.

Please read the enclosed leaflet before use.

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

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

PL 0635/0117
Dr Reddy’s Laboratories (UK) Ltd
29, Raeburn Rd, Beeston, NG9 2JS, UK
Each capsule contains chlordiazepoxide hydrochloride 5mg. Also contains lactose monohydrate. Capsules for oral use. Use as directed by the physician.

Please read the enclosed leaflet before use.
Do not store above 25°C. Store in the original package. Keep blister in the outer carton.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

POM

MHRA PAR – Chlordiazepoxide 5mg and 10mg Film-Coated Tablets

- 42 -
CHLORDIAZEPOXIDE 10MG FILM-COATED TABLETS
PL 08553/0110

LABELLING

Each capsule contains chlordiazepoxide hydrochloride 10mg. Also contains lactose monohydrate. Capsule for oral use. Use as directed by the physician. Please read the enclosed leaflet before use. Do not store above 25°C. Store in the original package. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
CHLORDIAZEPOXIDE 5MG CAPSULES
PL 08553/0070
Each film-coated tablet contains chlordiazepoxide 5mg as the hydrochloride. Also contains lactose monohydrate. Tablets for oral use. Use as directed by the physician. Please read the enclosed leaflet before use. Do not store above 25°C. Store in the original package. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Each film-coated tablet contains chlordiazepoxide 10mg as the hydrochloride.
Also contains lactose monohydrate. Tablets for oral use.
Use as directed by the physician.
Please read the enclosed leaflet before use.
Do not store above 25°C.
Store in the original package.
Keep blister in outer carton.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.