SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Chlordiazepoxide 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlordiazepoxide Hydrochloride 11.2 mg
Also contains lactose and sunset yellow E110, for a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet
Mid-green, round, biconvex film-coated tablets with MP4 engraved on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For short-term (2-4 weeks only) use:

- symptomatic relief of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
- Muscle spasm of varied aetiology
- Symptomatic relief of acute alcohol withdrawal

Not for use:

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

4.2 Posology and method of administration

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

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

Treatment should be given for the shortest possible duration.

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 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
Adults:
The starting dose should be 5 mg daily increasing to a usual dose of up to 30 mg in divided doses, but up to a maximum dose of 100 mg daily, in divided doses adjusted on an individual basis.

Treatment should always be as short as possible and should not continue at full dose for more than 2 weeks with a 2 week tapering off process.

Insomnia associated with anxiety
Adults:
10-30 mg at bedtime. Treatment should be as short as possible and normally varies from a few days to two weeks with a maximum of four weeks, including tapering off process.

Symptomatic relief of acute alcohol withdrawal
25-100 mg dose, repeated if necessary in 2-4 hours.

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

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

Children;
Chlordiazepoxide is 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

- Myasthenia gravis
- Hypersensitivity to the active substance, benzodiazepines or to any oof the excipients listed in section 6.1
- Acute pulmonary insufficiency: respiratory depression: sleep apnoea (risk of further respiratory depression)
- Severe hepatic insufficiency
- Obsessional states (inadequate evidence of safety and efficacy)
- Planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons – see section 4.6)

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

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.

Drug dependence, tolerance and potential for abuse

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse, or in patients with marked personality disorders. Therefore, regular monitoring in such patients is essential, regular repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for treatment with Chlordiazepoxide should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

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

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

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

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

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

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

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 will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, depression, nervousness, tension, restlessness, confusion, irritability, sleep disturbance, mood changes, sweating and diarrhoea. In severe cases the following symptoms may occur: derealisation (a feeling of unreality or of being separated from the body), confusional states, depersonalisation, hyperacusis, 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 dependant 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.

Rebound symptoms
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 (insomnia) and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually, (see section 4.2).

Duration of treatment
The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks 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. Moreover it is important that the patient should be made aware of the possibility of rebound phenomena, thereby minimising anxiety over such 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 within the dosage interval, especially when the dosage is high.

When chlordiazepoxide is being used it is important not to change 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
Extreme caution should be used in prescribing benzodiazepines to patients with marked personality disorders.

Reactions like restlessness, agitation, irritability, aggressiveness, excitement, confusion, 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.

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

Specific patient groups
The elderly should be given a reduced dose (see Posology).
Patients with phobias and/or chronic psychoses: Chlordiazepoxide is not recommended for the primary treatment of psychotic illness, (inadequate evidence of efficacy and safety).

Patients with depression: Chlordiazepoxide should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).
Patients with a history of alcohol and drug abuse: Chlordiazepoxide should be used with extreme caution in patients with a history of alcohol or drug abuse, (risk of abuse/dependence).

Intolerance to sugars
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Intolerance to colourants
Sunset yellow E 110 contained in these tablets can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended:
Alcohol: Chlordiazepoxide should not be used together with alcohol. The sedative effect may be enhanced when this product is used in combination with alcohol. This affects the ability to drive or use machines.
Sodium oxybate: avoid concomitant use (enhanced effects of sodium oxybate)
Take into account:
Centrally acting drugs: Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anaesthetics and sedative antihistamines. The elderly require special supervision.
Narcotic analgesics: enhancement of the euphoria may lead to an increased psychological dependence.
Anti-epileptic drugs: When chlordiazepoxide is used in conjunction with anti-epileptic drugs, side effects and toxicity may be more evident, particularly with hydantoins (e.g. phenytoin) and/or barbiturates, or combinations using them. This requires extra care in adjusting dosage in the initial stages of treatment.
Compounds which affect certain hepatic enzymes (particularly cytochrome P450):

- inhibitors (e.g. cimetidine) reduce clearance and may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation
- inducers (e.g. rifampicin) may increase clearance of benzodiazepines

Other drugs which enhance the sedative effects of chlordiazepoxide: cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants baclofen and tizanidine.
Antihypertensives, vasodilators & diuretics: enhanced hypotensive effect with ACE-inhibitors, adrenergic neurone blockers, alpha-blockers, angiotensin-II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, nitrates, hydralazine, minoxidil, moxonidine and sodium nitroprusside.
Dopaminergics: Benzodiazepines possibly antagonise the effects of levadopa.

4.6 Fertility, Pregnancy and lactation

Pregnancy:
Do not use during pregnancy, especially during the first and last trimesters, unless for compelling medical 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 trimesters. 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 the product is administered at high doses during the late phase of pregnancy or during labour, effects on the neonate, such as irregularities in the foetal heart rate, hypothermia, hypotonia, poor suckling 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.
Lactation:
Since benzodiazepines are found in breast milk, benzodiazepines should be avoided if possible by breast-feeding mothers.

4.7 Effects on ability to drive and use machines

Chlordiazepoxide may modify patients' performance at skilled tasks. Sedation, amnesia, impaired concentration, dizziness, blurred vision and impaired muscular function may occur and that, if affected, they should not drive or use machines, or take part in any activities where they 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 also Interactions).

Patients should be advised that alcohol may intensify any impairment, and should therefore be avoided during treatment.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

Common adverse effects include; Drowsiness and lightheadedness during the day, sedation, unsteadiness, 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, (see section 4.2).

Other adverse effects include; confusion, tremor, dysarthria, salivation changes and incontinence.

Rare adverse effects include; numbed emotions, reduced alertness, fatigue, headache, dizziness, muscle weakness, vertigo, or 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 using therapeutic dosages, the risk increasing at higher dosages. Amnesic affects 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.

Drug dependence (see section 4.4)
Use (even therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and precautions). Psychic dependence may occur.

Abuse of benzodiazepines has been reported, (see sections 4.2 and 4.4).

General disorders and administration site conditions:
Drug withdrawal symptoms (see 4.4 Special warnings and precautions).
Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of “rebound” phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.
In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients

with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants, as benzodiazepines potentiate the effects of other CNS depressants, (including alcohol).

Features:

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression, commonly 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:

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;

- maintain clear airway and adequate ventilation, if indicated
- gastric lavage – unnecessary if only benzodiazepine taken
- The value of gastric decontaminants is uncertain. Consider activated charcoal (50 g for an adult, 1g/kg for a child) within hour of ingestion if more than 1 mg/kg has been taken, provided the patient is not too drowsy
- The value of dialysis has not been determined.
- Supportive measures as indicated by the patient's clinical condition
- Special attention should be paid to respiratory and cardiovascular functions in intensive care.
- Rarely, flumazenil may be useful 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 almost 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

No relevant information additional to that contained elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Maize starch
Magnesium stearate
Lactose
Starch, pregelatinised

Coating:
Hypromellose
Ethylcellulose
Diethyl phthalate
Opaspray K-1F-3104 (hydroxypropyl cellulose, titanium dioxide, quinoline yellow E104, Patent blue V E131 and sunset yellow E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Containers: 36 months
Blister strips: 24 months

6.4 Special precautions for storage

Containers: Do not store above 25°C. Keep the container tightly closed and protect from light.
Blister strips: Do not store above 25°C. Store in the original package and protect from light.

6.5 Nature and contents of container

High density polystyrene containers with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.
250 micron PVC glass-clear/bluish rigid PVC pharmaceutical grade), 25 micron hard-tempered aluminium foil blister strips coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.

Pack size: 28, 30, 50, 56, 60, 84, 100,250,500 and 1000 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Genethics Europe Limited
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Klimentos Tower
Nicosia 1061
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PL 42976/0054

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