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2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Chlordiazepoxide base as the hydrochloride BP 5.6 mg

Excipient(s) with known effects
Also contains lactose
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety

Insomnia

Benzodiazipines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

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.

Method 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

Adults:

The starting dose should be 5 mg daily increasing to 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.

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.

Children : Not recommended.

Insomnia associated with anxiety *Adults:*

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

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.

Children : Not recommended.

4.3 Contraindications

Hypersensitivity to chlordiazepoxide or to any of the excipients listed in section 6.1; sleep apnoea syndrome; severe respiratory insufficiency; severe hepatic insufficiency; myasthenia gravis, acute pulmonary insufficiency.

4.4 Special warnings and Special 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

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 psychic.

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.

> 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 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

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.
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.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended: Concomitant intake with alcohol
The sedative effect may be enhanced when chlordiazepoxide is used in combination with alcohol. This will affect the ability to drive or operate machinery.

Take into account: Combination with CNS depressants

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic products, anaesthetics and sedative antihistamines.

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

Compounds which 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 sedation effect of chlordiazepoxide are: sisapride, lofexidine, nabilone, and the muscle-relaxants baclofen and tizanidine. Cimetidine inhibits the metabolism of chlordiazepoxide resulting in increased plasma concentration.

4.6 Fertility ,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).

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 during the day (when the product is used as a hypnotic it should be stated explicitly), numbed emotions, reduced alertness, confusion, fatigue, headache dizziness, muscle weakness, ataxia or double vision. The phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Other adverse reactions like gastrointestinal disturbances, changes in libido or skin reactions have been reported occasionally.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour.

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 the withdrawal or rebound phenomena (see warnings and precautions). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

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

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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.
Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include ataxia, hypotonia, hypotension, respiratory depression. Rarely coma, and very rarely death.
In the management of overdose it should be borne in mind that multiple agents may have been taken. 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.
As with other benzodiazepines, with chlordiazepoxide overdose should not present a threat to life unless combines with other CNS depressants (including alcohol).

5.1 Pharmacodynamic properties

Pharmacotherapeiutic group: Psycholeptics, anxiolytics, benzodiazepine derivatives. ATC code: N05BA02

Chlordiazepoxide acts as 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 metabolytes 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 metabolytes is significantly reduced.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Magnesium stearate
Lactose
Pregelatinised maize starch
Hydroxypropylmethylcellulose
Ethylcellulose
Diethylphthalate
Colours E131 and E132
Methanol
Methylene chloride

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months for containers, 24 months for blister packs.

6.4 Special precautions for storage

Store in a dry place below 25ºC.
Keep container well closed.

6.5 Nature and contents of container

A. High density polystyrene

B. Polypropylene 'Securitainer' or 'Snap Secure' type containers. Polythene bellows and/or polyurethane sponge wads.

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

Aluminium blister packs.

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

Not all pack size may be marketed.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

Chelonia Healthcare Limited
11 Boumpoulinas Street,
3rd floor, 1060 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 33414/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 December 1983 / 28 November 2008

10 DATE OF REVISION OF THE TEXT

23/01/2015