PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

CLOZYD 10 tablets

CLOZYD 20 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOZYD 10:

Each tablet contains 10 mg clobazam as the active ingredient.

Contains sugar (lactose monohydrate): 72,3 mg per tablet.

CLOZYD 20:

Each tablet contains 20 mg clobazam as the active ingredient.

Contains sugar (lactose monohydrate): 144,6 mg per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

CLOZYD 10 tablets:

White to off-white, modified capsule shaped, biconvex tablet, debossed with “13” and “25”’ on either side of functional scoreline on one side and plain on other side. The tablet should be free of all physical defects.

CLOZYD 20 tablets:

White to off-white, modified capsule shaped, biconvex tablet, debossed with “13” and “26” on either side of functional scoreline on one side and plain on other side. The tablet should be free of all physical defects.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLOZYD is used in the treatment of anxiety in neurotic patients and for pre-operative medicine. It may be effective in relieving the acute symptoms of alcohol withdrawal syndrome, but has no specific usefulness in the treatment of psychotic patients.

CLOZYD is only indicated when the disorder is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

The normal adult dose ranges between 10 mg and 30 mg daily: doses of 20 mg and above should preferably be given at bedtime or in divided doses.

For elderly and debilitated patients, as well as in children and patients with a low body mass, the daily dose should be halved.

Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and low initial doses and gradual dose increments, under careful observation, are required.

Treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.

Dosage and duration of treatment must be adjusted to the indication, the severity of the condition and the individual clinical response. Due regard must be paid to the possibility of interference with alertness and reaction time. The fundamental principle is to keep the dose as low as possible.

Patients with renal or hepatic impairment

Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and require low initial doses and gradual dose increments under careful observation (see section 4.4).

Secondary dose adjustment

After improvement of symptoms, the dose may be reduced.

Duration of treatment

The duration of treatment should be as short as possible. The patient should be reassessed after a period, not exceeding 4 weeks, and regularly thereafter in order to evaluate the need for continued treatment, especially where the patient is free of symptoms. The overall duration of treatment generally should not be more than 8 – 12 weeks, including a tapering off process. In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status, using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since it may lead to dependence (see section 4.4).

Discontinuation of treatment

It is strongly recommended that after prolonged treatment, CLOZYD is not withdrawn suddenly, but rather that the dose is reduced gradually under medical supervision; otherwise, withdrawal symptoms may occur (see section 4.4).

Method of administration

The 10 mg tablets can be divided into equal halves of 5 mg.

The 20 mg tablets can be divided into equal halves of 10 mg.

The tablets are to be swallowed with a generous amount of liquid (approximately 1 glass).

CLOZYD can be given with or without food.

4.3 Contraindications

- Known hypersensitivity to benzodiazepines, clobazam or any of the excipients of CLOZYD (see section 6.1).
- Patients with any history of drug or alcohol dependence (increased risk of development of dependence).

- Myasthenia gravis (risk of aggravation of muscle weakness).
- Severe respiratory insufficiency (risk of deterioration).
- Sleep apnoea syndrome (risk of deterioration).
- Severe impairment of liver function (risk of precipitating encephalopathy).
- During the first trimester of pregnancy (see section 4.6, for use during second and third trimester).
- Breastfeeding women (see section 4.6).
- Benzodiazepines must not be given to children without careful assessment of the need for their use. CLOZYD must not be used in children 3 years of age and younger.

4.4 Special warnings and precautions for use

Amnesia

Anterograde amnesia may occur with benzodiazepines. In case of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines, as in CLOZYD.

Muscle weakness

Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea, special observation is required, and a dose reduction may be necessary. CLOZYD is contraindicated in patients with myasthenia gravis or sleep apnoea syndrome (see section 4.3).

Suicidal ideation, suicide attempt, suicide and depression

Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression and treated with benzodiazepines and other hypnotics, including CLOZYD. However, a causal relationship has not been established (see section 4.8).

Personality disorders

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients

who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

Dependence

Benzodiazepines, including CLOZYD, may lead to physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment. However, this risk is present even with daily intake of CLOZYD over periods of only a few weeks and applies not only to possible abuse with particularly high doses but also to the therapeutic dose range. The risk of dependence is increased in patients with a history of alcohol or drug abuse. Therefore, the duration of treatment should be as short as possible (see section 4.2). The therapeutic benefit must be balanced against the risk of dependence during prolonged use. Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms which originally led to CLOZYD treatment.

This 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 be decreased gradually.

Once physical dependence has developed, abrupt termination of CLOZYD treatment will lead to withdrawal symptoms. These may include headaches, sleep disturbances, extreme anxiety, tension, restlessness, confusion, excitability and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hallucinations and symptomatic psychoses (e.g. withdrawal delirium), numbness and tingling sensations in the extremities, muscle pain, tremor, sweating, nausea, hyperacusis, hypersensitivity to light, noise and physical contact, as well as epileptic seizures.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, CLOZYD) to one with a short duration of action.

Serious skin reaction

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing experience.

The majority of the reported cases involved the concomitant use of other medicines, including antiepileptic medicines, that are associated with serious skin reactions.

SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. CLOZYD should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of CLOZYD should not be resumed and alternative therapy should be considered (see section 4.8).

Respiratory depression

CLOZYD is contraindicated in patients with severe respiratory insufficiency (see section 4.3).

Renal and hepatic impairment

In patients with impairment of renal or hepatic function, responsiveness to clobazam, as in CLOZYD, and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long-term treatment renal and hepatic function must be checked regularly.

Elderly patients

In elderly patients, due to the increased sensitivity to adverse reactions such as drowsiness, dizziness or muscle weakness, there is an increased risk of fall that may result in serious injury. A dose reduction is recommended.

Tolerance in epilepsy

In the treatment of epilepsy with benzodiazepines, including CLOZYD, consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment.

CYP2C19 poor metabolisers

In patients who are CYP2C19 poor metabolisers, levels of the active metabolite *N*-desmethylclobazam are expected to be increased as compared to extensive metabolisers. As this may lead to increased side effects, dosage adjustment of CLOZYD may be necessary (e.g. low starting dose with careful dose titration [see section 5.2]).

Concomitant use of cannabidiol

The concomitant use of CLOZYD with cannabidiol-containing medicines and non-medicinal products may result in increased exposure to *N*-desmethylclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Non-medicinal products containing cannabidiol must not be taken in combination with CLOZYD, as they contain unknown quantities of cannabidiol and are of variable quality (see sections 4.5 and 5.2).

Alcohol

It is recommended that patients abstain from drinking alcohol during treatment with CLOZYD (increased risk of sedation and other adverse effects) (see section 4.5).

Concomitant use of opioids and benzodiazepines

Concomitant use of opioids and benzodiazepines, including CLOZYD, may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and benzodiazepines for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe CLOZYD concomitantly with opioids, prescribe the lowest

effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation (see section 4.5).

CLOZYD is not recommended for the primary treatment of psychotic illness. In patients with depression or anxiety associated with depression, CLOZYD must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepines (such as CLOZYD) alone, can precipitate suicide in such patients.

Before treatment of anxiety states associated with emotional instability it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment.

In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for adjunctive treatment, i.e. not for primary treatment.

CLOZYD contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CLOZYD.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50 % (see section 5.2) and therefore increase the effects of CLOZYD, e.g. sedation (see section 4.5).

Central nervous system depressant medicines

Especially when CLOZYD is administered at higher doses, an enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant medicines, narcotic analgesics, anticonvulsant medicines, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

Opioids and other benzodiazepines

The concomitant use of benzodiazepines, as in CLOZYD, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive central nervous system (CNS) depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

Anticonvulsants

Addition of CLOZYD to established anticonvulsant medicine (e.g. phenytoin, valproic acid) may cause a change in plasma levels of these medicines. If used as an adjuvant in epilepsy, the dosage of CLOZYD should be determined by monitoring the electroencephalogram (EEG) and the plasma levels of the other medicines checked.

Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam, as in CLOZYD, to the active metabolite *N*-desmethylclobazam.

Stiripentol increases plasma levels of clobazam, as in CLOZYD, and its active metabolite *N*-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels of clobazam and the active metabolite is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately. Clinical monitoring is recommended and dose adjustment may be necessary.

Narcotic analgesics

If CLOZYD is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

Muscle relaxants

The effects of muscle relaxants, analgesics and nitrous oxide may be enhanced.

CYP2C19 inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to *N*-

desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (see section 5.2).

Cannabidiol

When cannabidiol and CLOZYD are co-administered, bidirectional pharmacokinetic interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of *N*-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in the dose of clobazam should be considered if somnolence or sedation is experienced when CLOZYD is co-administered with cannabidiol.

CYP2D6 substrates

Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of medicines metabolised by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of clobazam in pregnant women. Nevertheless, a large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of major malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidence of cleft lip and palate were observed in case-control studies.

CLOZYD is not recommended during pregnancy and in women of childbearing potential not using contraception.

Clobazam, as in CLOZYD, crosses the placenta. Animal studies have demonstrated reproductive toxicity.

Women of childbearing potential should be informed to contact their medical practitioner regarding

discontinuation of the product if they are pregnant or intend to become pregnant. CLOZYD must not be used in the first trimester of pregnancy (see section 4.3). If CLOZYD treatment is to be continued, use clobazam at the lowest effective dose.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

If CLOZYD is used during the late phase of pregnancy or during childbirth, effects on the neonate, such as respiratory depression (including respiratory distress and apnoea), sedation signs, hypothermia, hypotonia and feeding difficulties in the newborn (so-called “floppy infant syndrome”) are to be expected.

Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy, may have developed physical dependence and may be at risk of developing a withdrawal syndrome in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breastfeeding

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

Fertility

No clinical data on fertility are available. In a fertility animal study in male and female rats, no effect on fertility was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

CLOZYD may cause adverse effects (e.g. sedation, amnesia, impaired concentration or muscle weakness, see section 4.8) that may impair the patient’s ability to concentrate and react.

If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

CLOZYD can impair cognitive function and can affect a patient’s ability to drive safely.

Patients should therefore be warned to not drive a vehicle, operate machinery or perform tasks requiring their attention, until they know how CLOZYD will affect them.

4.8 Undesirable effects

Blood and lymphatic system disorders

Frequency unknown: blood dyscrasias have been reported

Metabolism and nutrition disorders

Frequent: decreased appetite

Psychiatric disorders

Frequent: irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), drug tolerance (especially during prolonged use, see section 4.4), acute agitation

Less frequent: abnormal behaviour, confusional state, anxiety, delusion, nightmares, loss of libido (particularly with high doses or in long-term treatment, and is reversible)

Frequency unknown: dependence (especially during prolonged use, see section 4.4), initial insomnia, anger, fits of rage, nightmares, hallucinations, psychotic disorder, poor sleep quality, difficulty in falling asleep or sleeping through, suicidal ideation or tendencies. In the event of such reactions, treatment with CLOZYD must be discontinued.

Pre-existing depression may be unmasked during benzodiazepine use.

Tolerance and dependence may develop, especially during prolonged use (see section 4.4).

Nervous system disorders

Frequent: tiredness and sleepiness (somnolence), especially at the beginning of treatment and when higher doses are used, sedation, dizziness, disturbance in attention, slow speech/dysarthria/speech disorder (particularly with high doses or in long-term treatment, and is reversible), headache, tremor, ataxia or a fine tremor of the fingers may occur

Less frequent: numbed emotions, emotional poverty, anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels, amnesia effects may be associated with inappropriate behaviour, memory impairment

Frequency unknown: slowed reaction time, drowsiness*, disorientation and confusion, muscle weakness, lethargy, cognitive disorder, impairment of consciousness (sometimes combined with respiratory disorders, may occur in very rare cases, particularly in elderly patients; these effects sometimes persist for a considerable length of time, may be combined with respiratory disorders), nystagmus (particularly with high doses or in long-term treatment), unsteadiness of gait and other motor functions (such reactions occur particularly with high doses or in long-term treatment, and are reversible)

*drowsiness occurs more frequently in elderly and debilitated patients and in patients receiving high doses.

Eye disorders

Less frequent: visual disorders (diplopia), such reactions occur particularly with high doses or in long-term treatment and is reversible

Respiratory, thoracic and mediastinal disorders

Frequency unknown: respiratory depression (especially if administered in high doses), respiratory failure (particularly in patients with pre-existing compromised respiratory function, e.g. in patients with bronchial asthma or brain damage, see sections 4.3 and 4.4)

Gastrointestinal disorders

Frequent: dry mouth, decreased appetite, nausea/vomiting, constipation

Hepato-biliary disorders

Frequency unknown: hepatic dysfunction

Skin and subcutaneous tissue disorders

Less frequent: cutaneous reactions, such as rash

Frequency unknown: photosensitivity reaction, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcomes)

Musculoskeletal and connective tissue disorders

Frequency unknown: muscle spasms, muscle weakness

General disorders and administration site conditions

Frequent: fatigue, especially at the beginning of treatment and when higher doses are used

Less frequent: increased body mass (particularly with high doses or in long-term treatment, and is reversible)

Frequency unknown: slow response to stimuli, hypothermia

Injury, poisoning and procedural complications

Less frequent: fall.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of CLOZYD is important. It allows continued monitoring of the benefit/risk balance of CLOZYD. Health care providers are asked to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Signs and symptoms

Overdose and intoxication with benzodiazepines, including CLOZYD, may lead to central nervous system depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension and, rarely, coma. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including alcohol.

Management

In the management of intoxication, it is recommended that the possible involvement of multiple medicines be taken into consideration.

Intravenous fluid replenishment and general supportive measures may be indicated in addition to monitoring of consciousness, respiration, pulse rate and blood pressure.
Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6 Tranquillisers.

Pharmacotherapeutic group: Benzodiazepine derivatives.

ATC Code: N05BA.

Clobazam is a 1,5-benzodiazepine, with anxiolytic properties.

5.2 Pharmacokinetic properties

Absorption

After oral administration, clobazam is rapidly and extensively absorbed. Time to peak plasma concentrations (T_{max}) is achieved from 0,5 – 4,0 hours. The administration of clobazam tablets with food or crushed in applesauce slows the rate of absorption by approximately 1 hour, but it does not affect the overall extent of absorption. Clobazam can be given without regard to meals.
Concomitant intake of alcohol can increase the bioavailability of clobazam by 50 %.

Distribution

After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 – 709 ng/mL) was observed after 0,25 – 4 hours. Clobazam is lipophilic and distributes rapidly throughout the body. Based on a population pharmacokinetic analysis, the apparent volume of distribution at steady-state was approximately 102 L, and is concentration independent over the therapeutic range. Approximately 80 – 90 % of clobazam is bound to plasma protein.

Clobazam accumulates approximately 2 – 3-fold to steady-state while the active metabolite *N*-desmethylclobazam (*N*-CLB) accumulates approximately 20-fold following clobazam twice daily administration. Steady state concentrations are reached within approximately 2 weeks.

Biotransformation

Clobazam is rapidly and extensively metabolised in the liver.

Clobazam metabolism occurs primarily by hepatic demethylation to *N*-desmethylclobazam (*N*-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. *N*-CLB is an active metabolite and the main circulating metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-*N*-desmethylclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolisers exhibit a 5-fold higher plasma concentration of *N*-CLB compared to extensive metabolisers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan led to increases of 90 % in AUC and 59 % in C_{max} values for dextromethorphan.

Concomitant administration of 400 mg ketoconazole (CYP3A4 inhibitor) increased clobazam AUC by 54 % with no effect on C_{max}.

These changes are not considered clinically relevant.

Elimination

Based on a population pharmacokinetic analysis, plasma elimination half-lives of clobazam and *N*-CLB were estimated to be 36 hours and 79 hours, respectively.

Clobazam is cleared mainly by hepatic metabolism with subsequent renal elimination. In a mass balance study, approximately 80 % of the administered dose was recovered in urine and about 11 % in the faeces. Less than 1 % of unchanged clobazam and less than 10 % of unchanged *N*-CLB are excreted through the kidneys.

Special populations

Clobazam crosses the placental barrier and appears in breast milk. Both in the fetal blood and in breast milk, effective concentrations may be reached.

Elderly patients

In elderly patients, there is a tendency to a reduction in clearance following oral administration; terminal half-life is prolonged and the distribution volume increased. This may lead to a more extensive accumulation of the medicine when administered on a multiple-dose basis, than in younger subjects. The effect of age on the clearance and accumulation profile of clobazam seems also to apply to the active metabolite.

Hepatic impairment

In patients with severe liver disease, the distribution volume of clobazam is increased and the terminal half-life is prolonged.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Lactose monohydrate

Magnesium stearate

Maize starch

Talc.

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in original container until required for use.

6.5 Nature and contents of container

Opaque white 60 mL HDPE bottle, with a 33 mm child-resistant closure, inserted into an outer cardboard carton.

Pack size: 100 tablets.

Silver aluminium foil/clear transparent PVC/PVdC blister strip (containing 10 x 10 tablets), inserted into an outer cardboard carton.

Pack size: 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

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Building B, Ground Floor

22 Karee Street

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8. REGISTRATION NUMBERS

CLOZYD 10: 56/2.6/1077

CLOZYD 20: 56/2.6/1078

9. DATE OF FIRST AUTHORISATION

19 November 2024

10. DATE OF REVISION OF THE TEXT

Not applicable.