SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

CLOBAZAM 10 ADCO , 10 mg, tablets

CLOBAZAM 20 ADCO , 20 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CLOBAZAM 10 ADCO : Each tablet contains 10 mg of clobazam.

Excipient(s) with known effect: Each tablet contains 92 mg of lactose monohydrate.

CLOBAZAM 20 ADCO : Each tablet contains 20 mg of clobazam.

Excipient(s) with known effect: Each tablet contains 184 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CLOBAZAM 10 ADCO , tablets.

White to off white, oval shaped, uncoated tablets with functional score on one side and “C” and “M” debossed on the other side.

CLOBAZAM 20 ADCO , tablets.

White to off white, oval shaped, uncoated tablets with functional score on one side and “C” and “L” debossed on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

CLOBAZAM ADCO 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 – 30 mg daily – doses of 20 mg and above should preferably be given at bedtime or divided doses.

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

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. 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 status.

Special populations

Elderly

For elderly, debilitated and light-weight patients, 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.

Paediatric Population

The daily dose should be halved for children.

The dose should be taken orally with a small amount of liquid as appropriate.

4.3 Contraindications

- In patients with hypersensitivity to benzodiazepines or any of the excipients of CLOBAZAM ADCO (refer to section 6.1).
- In patients with any history of drug or alcohol dependence (increased risk of development of dependence).
- In patients with myasthenia gravis (risk of aggravation of muscle weakness).

- In patients with severe respiratory insufficiency (risk of deterioration).
- In patients with sleep apnoea syndrome (risk of deterioration).
- In patients with severe hepatic insufficiencies (risk of precipitating encephalopathy).
- During the first trimester of pregnancy (for use during second and third trimester, refer to section 4.6).
- In breastfeeding women.
- Benzodiazepines must not be given to children without careful assessment of the need for their use. CLOBAZAM ADCO must not be used in children under 3 years.

4.4 Special warnings and precautions for use

Amnesia

Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines.

Muscle weakness

CLOBAZAM ADCO 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. CLOBAZAM ADCO is contraindicated in patients with myasthenia gravis.

Depression and 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.

Paradoxical reactions such as acute hyperexcitable states with rage may occur – if these occur, CLOBAZAM ADCO should be discontinued.

Dependence

Use of benzodiazepines – including CLOBAZAM ADCO – may lead to the development of physical and psychic 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. Therefore, the duration of treatment should be as short as possible (refer to section 4.2).

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms which originally led to CLOBAZAM ADCO treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Other symptoms due to abrupt withdrawal may include headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability.

In severe cases after abrupt termination the following symptoms may occur derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, CLOBAZAM ADCO) 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 ADCO in both children and adults during the post-marketing experience. A majority of the reported cases involved the concomitant use of other medicines, including anti-epileptic 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. CLOBAZAM ADCO should immediately be discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of this medicine should not be resumed and alternative therapy should be considered (refer to section 4.8).

Respiratory depression

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of CLOBAZAM ADCO may be necessary. CLOBAZAM ADCO is contraindicated in patients with severe respiratory insufficiency (refer to section 4.3).

Renal and hepatic impairment

In patients with impairment of renal or hepatic function, responsiveness to CLOBAZAM ADCO 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.

Blood dyscrasias and hepatic dysfunction have been reported.

Elderly patients

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

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 CLOBAZAM ADCO may be necessary (e.g. low starting dose with careful dose titration (refer to section 5.2)).

Alcohol

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

Concomitant use of opioids and benzodiazepines

Concomitant use of opioids and benzodiazepines, including CLOBAZAM ADCO, may results 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 CLOBAZAM ADCO 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 (refer to section 4.5).

Concomitant use of barbiturates, antihistamines, narcotics or other central nervous system depressants

There is an additive risk of central nervous system depression when these medicines are taken together (refer to section 4.5). Large doses may produce syncope.

Duration of treatment

The duration of treatment should be as short as possible (refer to section 4.2) but should not exceed eight to twelve weeks in case of anxiety, including the 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 aware of the possibility of rebound phenomena, thereby a minimising anxiety over such symptoms, should they occur while the product is being discontinued.

CLOBAZAM ADCO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take CLOBAZAM ADCO.

4.5 Interaction with other medicines and other forms of interaction

Alcohol

Concomitant consumption of alcohol can increase the bioavailability of CLOBAZAM ADCO by 50% (refer to section 5.2) and therefore increase the effects of CLOBAZAM ADCO e.g. sedation (refer to section 4.5).

Central nervous system depressant medicines

Especially when CLOBAZAM ADCO 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 agents, narcotic analgesics, anti-convulsant medicines, anaesthetics and sedative antihistamines. Special caution is also necessary when CLOBAZAM ADCO is administered in cases of intoxication with such substances or with lithium.

Opioids

The concomitant use of benzodiazepines, including CLOBAZAM ADCO, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit the dosage and duration of concomitant use of benzodiazepines and opioids (refer to section 4.4).

Anti-convulsants

Addition of CLOBAZAM ADCO to established anticonvulsant medication (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 CLOBAZAM ADCO should be determined by monitoring the EEG and the plasma levels of the other medicines checked.

Phenytoin and carbamazepine may cause an increase in the metabolic conversion of CLOBAZAM ADCO to the active metabolite N-desmethylclobazam.

Stiripentol increases plasma levels of CLOBAZAM ADCO and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels of CLOBAZAM ADCO and active metabolite is recommended, prior to initiation of stiripentol, and then again 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 CLOBAZAM ADCO 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.

CYP 2C19 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 ADCO may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (refer to section 5.2).

CYP 2D6 substrates

CLOBAZAM ADCO 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 is limited amount of data from the use of CLOBAZAM ADCO 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 of benzodiazepines during the first trimester of pregnancy, although incidence of cleft lip and palate were observed in case-control studies.

CLOBAZAM ADCO is not recommended during the first trimester of pregnancy and in women of childbearing potential not using contraception.

CLOBAZAM ADCO crossed the placenta. Animal studies have demonstrated reproductive toxicity.

Women of childbearing potential should be informed of the risks and benefits of the use of CLOBAZAM ADCO during pregnancy.

Women of childbearing potential should be informed to contact her medical practitioner regarding discontinuation of the product if they are pregnant or intend to become pregnant. If CLOBAZAM ADCO treatment is to be continued, use CLOBAZAM ADCO at the lowest effective dose.

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

Administration of CLOBAZAM ADCO before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnoea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the newborn (signs and symptoms of the so-called “floppy infant syndrome”). In the later stages of pregnancy, it must only be used if there are compelling indications.

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 for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breastfeeding

Since CLOBAZAM ADCO passes into the breastmilk, it should not be given to breastfeeding mothers.

Fertility

No clinical data on fertility are available. In a fertility study in male and female rats no effect on fertility was observed.

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 (refer to section 4.5).

CLOBAZAM ADCO can impair cognitive function and can affect a patient's ability to drive safely. Patients should be advised particularly at the initiation of therapy, not to drive motor-vehicles, climb dangerous heights, or operate dangerous machinery. In these situations, impaired decision making could lead to accidents.

When prescribing CLOBAZAM ADCO, patients should be told:

- CLOBAZAM ADCO is likely to affect your ability to drive.
- Do not drive until you know how CLOBAZAM ADCO affects you.

4.8 Undesirable effects

Metabolism and nutrition disorders

Frequent: decreased appetite

Psychiatric disorders

Frequent: irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), medicine tolerance (especially during prolonged use) (refer to section 4.4), agitation

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

Frequency not known: dependence (especially during prolonged use) (refer to section 4.4), initial insomnia, anger, hallucination, psychotic disorder, poor sleep quality, suicidal ideation

Nervous system disorders

Frequent: 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

Less frequent: emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia (in the normal dose range, but especially at higher dose levels), depression of mood and affect, lethargy, increased motor activity, decreased motor activity, paradoxical reactions such as hyperexcitable state with rage may occur.

Frequency not known: cognitive disorder, altered state of consciousness (particularly in elderly patients, may be combined with respiratory disorders), nystagmus (particularly with high doses or in long term treatment), gait disturbance (particularly with high doses or in long term treatment, and is reversible)

Eye disorders

Less frequent: diplopia (particularly with high doses or in long term treatment, and is reversible)

Respiratory, thoracic and mediastinal disorders

Frequency not known: respiratory depression, respiratory failure particularly in patients with pre-existing compromised respiratory function e.g. in patients with bronchial asthma or brain damage (refer to section 4.3 and 4.4)

Gastrointestinal disorders

Frequent: dry mouth, nausea, constipation

Skin and subcutaneous tissue disorders

Less frequent: rash

Frequency not known: photosensitivity reaction, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome)

Musculoskeletal and connective tissue disorders

Frequency not known: 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: weight increase (particularly with high doses or in long-term treatment, and is reversible)

Frequency not known: slow response to stimuli, hypothermia

Injury, poisoning and procedural complications

Less frequent: fall

Blood dyscrasias and hepatic dysfunction have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Manifestations of overdosage include somnolence, confusion, coma, respiratory and cardiovascular depression and hypotension.

Following overdose with oral benzodiazepines activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective. Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives. ATC code: N05BA09.

Mechanism of action

Clobazam is a 1,5-benzodiazepine. In single doses up to 20 mg or in divided doses up to 30 mg, clobazam does not affect psychomotor function, skilled performance, memory or higher mental functions.

5.2 Pharmacokinetic properties

Absorption

After oral administration, clobazam is rapidly and extensively well absorbed. Time to peak plasma concentrations (Tmax) is achieved from 0,5 – 4,0 hrs. 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 metabolizers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolizers.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide

Corn starch

Hydroxy propyl cellulose

Lactose monohydrate

Magnesium stearate

Talc

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in the original container.

6.5 Nature and contents of container

100's count bottle pack for CLOBAZAM 10/20 ADCO

40 ml HDPE container, utilizing 33 mm child resistant (CR) closure with induction sealing wad. Puritan cotton coil 9 grm/yard.

1000's count bottle pack for CLOBAZAM 10 ADCO

250 ml HDPE containers, utilizing 53 mm continuous thread (CT) Screw cap closure with induction sealing wad. Puritan cotton coil 9 grm/yard.

1000's count bottle pack for CLOBAZAM 20 ADCO

400 ml HDPE containers, utilizing 53 mm continuous thread (CT) Screw cap closure with induction sealing wad. Puritan cotton coil 9 grm/yard.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Customer Care: 0860 ADCOCK/232625

8. REGISTRATION NUMBER(S)

CLOBAZAM 10 ADCO: 55/2.6/0546

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27 June 2023

10. DATE OF REVISION OF THE TEXT

adcock ingram

PI D032335-01 09/2023