For the use only of a Registered Medical Practitioners or a Hospital or a Laboratory

Generic Name CLOBAZAM

Trade Name CLOBAKEM

ALKEM

1. NAME OF THE MEDICINAL PRODUCT: Clobazam tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Each uncoated tablet contains:
Clobazam IP……5mg

Each uncoated tablet contains:
Clobazam IP……10mg

3. PHARMACEUTICAL FORM: Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications:

Clobazam is a 1,5-benzodiazepine indicated for the short-term relief (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness. The use of Clobazam to treat short-term "mild" anxiety is inappropriate and unsuitable.

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. Indeed, in patients with anxiety associated with depression, Clobazam must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as Clobazam) alone, can precipitate suicide in such patients.

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

Clobazam may be used as adjunctive therapy in epilepsy.

4.2 Posology and Method of Administration:

Treatment of anxiety

The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety.
The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced.

It should not be used for longer than 4 weeks. Long term chronic use as an anxiolytic is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Clobazam for a long time may require a longer period during which doses are reduced.

Elderly:
Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

Treatment of epilepsy in association with one or more other anticonvulsants
Adults:
In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily.

Paediatric patients aged 6 years and above:
When prescribed for children treatment requires low initial doses and gradual dose increments under careful observation. It is recommended that normally treatment should be started at 5mg daily. A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendations can be made in children under 6 years of age.

Tablets can be administered whole, or crushed and mixed in apple sauce. The 10mg tablets can be divided into equal halves of 5mg. Clobazam can be given with or without food.

The patient must be re-assessed after a period not exceeding 4 weeks and regularly thereafter in order to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage.

4.3 Contraindications:
Clobazam must not be used:
− In patients with hypersensitivity to benzodiazepines or any of the excipients of Clobazam.
− 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
− In breast-feeding women.
Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication.

4.4 Special Warnings and Special 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 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 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.

• Dependence

Use of benzodiazepines - including clobazam - 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.

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 treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

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

A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs 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 should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

• Respiratory Depression

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of clobazam may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency.

• Renal and hepatic impairment

In patients with impairment of renal or hepatic function, responsiveness to clobazam 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 the elderly, due to the increased sensitivity to adverse reactions such as drowsiness, dizziness, 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 clobazam - 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 clobazam may be necessary (e.g. low starting dose with careful dose titration.

• Alcohol
It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects)

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

- **Alcohol**

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% and therefore increase the effects of clobazam e.g. sedation

• Central nervous system depressant drugs
Especially when clobazam 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, anticonvulsant drugs, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

• Anticonvulsants
Addition of clobazam to established anticonvulsant medication (eg, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of Clobazam should be determined by monitoring the EEG and the plasma levels of the other drugs checked.

Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethyl clobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels of clobazam and 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 clobazam 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 nitrious 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 may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors.

• **CYP 2D6 substrates**
Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol may be necessary.

4.6 Fertility, Pregnancy and Lactation
There are limited amount of data from the use of Clobazam in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In animal studies, no congenital malformations have been found in mice, rats and rabbits.

In the post-marketing safety database, limited data on exposed pregnancies are available with clobazam. Some of those cases reported fetal or neonatal disorders.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant.
Administration of clobazam before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the new born (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.

As a precautionary measure it is preferable to avoid the use of clobazam during pregnancy. Clobazam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

4.7 Effects on Ability to Drive and Use Machines
Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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.

4.8 Undesirable Effects

• *Nervous system disorders*
Clobazam may cause sedation, leading to fatigue and sleepiness, especially at the beginning of treatment and when higher doses are used. Slowing of reaction time, drowsiness, numbed emotions, confusion, headaches, dizziness, muscle weakness, ataxia or a fine tremor of the fingers may occur.

Slowed or indistinct speech (disorders of articulation), unsteadiness of gait and other motor functions or loss of libido may occur. Such reactions occur particularly with high doses or in long-term treatment, and are reversible.

After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, may occur in very rare cases, particularly in elderly patients: these effects sometimes persist for some length of time. These disorders have not been seen so far under clobazam treatment.

Anterograde amnesia may occur, especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour.

• *Psychiatric disorders*
Especially in the elderly and in children, paradoxical reactions, may occur such as restlessness, irritability, difficulty in falling asleep or sleeping through, irritability, acute agitational states, anxiety, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies or frequent muscle spasms. In the event of such reactions, treatment with clobazam must be discontinued.

Pre-existing depression may be unmasked during benzodiazepine use.

Tolerance and physical and/or psychic dependence may develop, especially during prolonged use. Discontinuation of the therapy may result in withdrawal or rebound phenomena. Abuse of benzodiazepines has been reported.
When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness.
As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

• *Eye disorders*
Visual disorders (diplopia, nystagmus). Such reactions occur particularly with high doses or in long-term treatment, and are reversible.

• *Respiratory, thoracic and mediastinal disorders*
Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (i.e., in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate.

• *Gastrointestinal disorders*
Dry mouth, constipation, decreased appetite, nausea

• *Skin and subcutaneous tissue disorders*
Cutaneous reactions, such as rash or urticarial may develop in very rare cases. Stevens-Johnson syndrome, Toxic Epidermal Necrolysis

• *Metabolism and nutrition disorders*
Weight gain, may occur particularly with high doses or in long-term treatment. This reaction is reversible.

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.

Following overdose with oral benzodiazepines, 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.

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

Clobazam is a 1,5-benzodiazepine. In single doses up to 20mg or in divided doses up to 30mg, 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 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 to 709 ng/ml) was observed after 0.25 to 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.

• ***Metabolism***
Clobazam is rapidly and extensively metabolized 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.

5.3 Preclinical Safety Data
Carcinogenesis: The carcinogenic potential of clobazam has not been adequately assessed. In a limited study in rats, oral administration of clobazam (4, 20, and 100 mg/kg/day) for 2 years resulted in an increased incidence of thyroid follicular cell adenomas in males at the high dose.

Mutagenesis: Clobazam and the major active metabolite, N-desmethylclobazam, were negative for genotoxicity, based on data from a battery of in vitro (bacteria reverse mutation, mammalian clastogenicity) and in vivo (mouse micronucleus) assays.

6. PHARMACEUTICAL PARTICULARS

6.1 Shelf-life: 36 Months

6.2 Special Precautions for Storage: Store in a cool dry place protected from light

6.3 Nature and Contents of Container: 2 X 5Combi Blister strip of 10 Tablets

Marketed By:
Alkem Laboratories Limited,
Alkem House, S.B. Road,
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