

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zacco 5mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral suspension contains 5mg clobazam.

Excipient(s) with known effect:

Each 5ml of oral suspension contains 7.5mg of methyl parahydroxybenzoate (E218).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

White to off-white viscous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Zacco is a 1,5-benzodiazepine indicated in adults for the short-term symptomatic treatment (2-4 weeks) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress.

In treatment of anxiety states associated with affective disorders Zacco must be used only in conjunction with adequate treatments for the underlying disorder.

In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for short term symptomatic management of hyperarousal and agitation. Benzodiazepines do not possess antipsychotic properties.

Zacco may be used as adjunctive therapy in epilepsy, in adults and children over 2 years if standard treatment with one or more anticonvulsants has failed. Treatment of simple or complex partial epilepsy with or without secondary generalisation and treatment of all types of generalised epilepsy (tonic / clonic, myoclonic, absence seizures).

4.2 Posology and method of administration

Posology

Prior to starting treatment with Clobazam Thame, a discussion should be held with patients to put in place a strategy for ending treatment with Clobazam Thame 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. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Treatment of anxiety:

Treatment should be as short as possible. 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, especially where the patient is free of symptoms. Generally the overall duration of treatment (i.e. including tapering-off process) must not exceed 8 to 12 weeks.

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 with special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence.

Adults:

The usual anxiolytic dose for adults is 20-30mg 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.

Due regard must be paid to the possibility of interference with alertness and reaction time.

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 Zacco for a long time may require a longer period during which doses are reduced.

Elderly:

Doses of 10-20mg 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 5-15mg/day is recommended with increases of 10mg increments, increasing as necessary up to maximum of 60mg daily.

Elderly:

In elderly patients in the management of epilepsy with clobazam increased response and increased susceptibility to adverse reactions may occur. These patients require low initial doses with gradual increases under careful observation.

Paediatric population aged 2 years and above:

Zacco doses should be adapted individually. Doses can be taken once a day, or as 2 to 3 divided doses, keeping the total daily dose the same.

When prescribed for children, treatment requires low initial doses and gradual dose increments under careful observation. Clobazam is typically initiated at a low dose, initially in children aged 6 years and above 5 mg/day or 0.1 mg/kg/day for younger patients. The dose may be increased slowly by steps of 0.1 to 0.2 mg/kg/day at 7 days intervals, until the required clinical effect is achieved or side effects occur.

Studies have suggested that slow titration may help to avoid adverse effects and that when present side effects may be reduced or eliminated with dose reduction,

The following up-titration has been proposed in the literature in order to take into account the high metabolism variability linked to the P450 system maturation - especially in the presence of inducers and inhibitors - and should be used with increase of dose by 0.1 to 0.2mg/kg every week up to the target dose.

A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

Paediatric population aged 1 month -2 years:

There is a lack of data regarding the use of the product in patients under 2 years old Zacco should not be used as an anticonvulsant treatment in children from 1 months to 2 years old unless under exceptional situations when there is a clear epilepsy indication. The starting dose in this exceptional circumstance should be the lowest one (0.1mg/kg/day) and titration should be more cautious, not more than 0.1mg/kg/day as in this population the metabolic pathways for clobazam may not be fully mature. Up-to-date no precise dosage recommendations can be made for this population.

During adjunctive therapy in epilepsy, in adults and children aged two years and above, the patient must be re-assessed after a period not exceeding 4 weeks and every 4 weeks 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), it is recommended to gradually decrease the dosage since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment.

Hepatic and renal impairment (all indications):

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. The maximum dose should not be exceeded.

Zacco Oral Suspension is particularly recommended for children and adults with swallowing difficulties as it allows a secure and precise dosage.

The patient should be checked regularly at the start of the treatment in order to decrease if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

Method of administration

For oral use only.

Zacco can be given with or without food.

This product may settle during storage. Shake the bottle well before use.

4.3 Contraindications

Zacco must not be used:

- In patients with hypersensitivity to clobazam, benzodiazepines or any of the excipients listed in 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).
- In breast-feeding women.

Benzodiazepines must not be given to children without careful assessment of the need for their use. Zacco should not be used in children from 1 month to 2 years old unless under exceptional situations as an anticonvulsant treatment where there is a clear epilepsy indication.

4.4 Special warnings and precautions for use

Switching between formulations

In some individuals taking Zacco, clobazam reaches higher plasma levels than the same dose taken as a tablet. This may lead to an increased risk of respiratory depression and sedation, which may be most noticeable when switching to this medicine from tablets. Therefore, caution must be taken when switching between clobazam products.

Children under 2 years

There is a lack of data regarding the use of the product in patients under 2 years old. For this reason, careful assessment and monitoring is required by the treating physician for use in children under 2 years for anticonvulsant treatment.

Amnesia

Benzodiazepines 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).

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.

Duration of treatment

The duration of treatment should be as short as possible (see Posology). Extension beyond these periods should not take place without reevaluation 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 minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When benzodiazepines with a long duration of action are being used (for example Zacco) it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

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. Before treatment of anxiety states associated with affective disorders, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. In patients with anxiety associated with depression, clobazam must be used only in conjunction with adequate treatments for the underlying disorder. Use of benzodiazepine (such as clobazam) alone, can precipitate suicide in such patients.

Patients with schizophrenic or other psychotic illnesses

Benzodiazepines are not recommended for the primary treatment of patients with schizophrenic or other psychotic illnesses.

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. (See section 4.8). They are more likely to occur in children and the elderly. Should this occur, use of the medicinal product should be discontinued.

Suicidal ideation/suicide attempt/ suicide and depression

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for clobazam.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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 clobazam. However, a causal relationship has not been established (see section 4.8).

Drug dependence, tolerance and potential for abuse

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 Clobazam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

. 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 (see section 4.2).

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.

Drug withdrawal syndrome

Prior to starting treatment with Clobazam, 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 Clobazam 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, and for use in epilepsy).

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.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, Zacco) 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 (see 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 may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (please refer to section 4.3).

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. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

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

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

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-desmethyloclobazam 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 (please refer to section 5.2)).

Alcohol

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

Benzodiazepines including clobazam, should be used with extreme caution in patients with a history of alcohol or drugs abuse.

Risk from concomitant use of opioids and benzodiazepines

Concomitant use of Zacco and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Zacco with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Zacco concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Concomitant use of cannabidiol

The concomitant use of clobazam with cannabidiol-containing medicinal and nonmedicinal products may result in increased exposure to N-desmethyloclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Nonmedicinal products containing cannabidiol must not be taken in combination with Clobazam as they contain unknown quantities of cannabidiol and are of variable quality (see Section 4.5, and 5.2)

Excipients warning

This medicinal product contains **methyl parahydroxybenzoate** (E218), which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1mmol **sodium** (23mg) per 5ml dose, that is to say essentially 'sodium-free'.

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 (please refer to section 4.5). This affects the ability to drive or use machines.

Central nervous system depressant drugs

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Zacco with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant. The dosage and duration of concomitant use should be limited (see section 4.4).

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 Zacco 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 which may result in adverse reactions.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately.

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 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 may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (Please refer to Section 5.2).

Cannabidiol

When cannabidiol and clobazam are co-administered, bi-directional PK 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 drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in dose of clobazam

should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.

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.

Cytochrome P-450 enzyme inhibitors

Concomitant administration of medicinal products that inhibit the Cytochrome P-450 enzyme system, such as cimetidine and erythromycin, can enhance and prolong the effects of clobazam.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of 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 incidences of cleft lip and palate were reported in certain case-control studies.

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

Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3).

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

Women of childbearing potential should be informed to contact her physician regarding discontinuation of the product if they are pregnant or intend to become pregnant. If clobazam treatment is continued, it should be used 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 clobazam is administered during the late phase of pregnancy or during childbirth, effects on the neonate, such as respiratory depression (including respiratory distress and apnea), 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.

Breast-feeding

Since benzodiazepines are found in the breast milk, benzodiazepines must not be given to breast feeding mothers (see section 4.3).

Fertility

No clinical data on fertility are available. In a fertility 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

Clobazam has major influence on the 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 section 4.5). Patients should not drive or use machinery until it is verified that the ability to perform these activities is not affected.

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

Metabolism and nutrition disorders

Common: **decreased appetite**

Psychiatric disorders

Common: **irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), drug tolerance** (especially during prolonged use), **agitation**

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

Not known: **dependence** (especially during prolonged use), **initial insomnia, anger, hallucination, psychotic disorder, poor quality sleep, suicidal ideation, drug dependence** (see section 4.4)

Nervous system disorders

Very common: **somnolence**, especially at the beginning of treatment and when higher doses are used

Common: **sedation, dizziness, disturbance in attention, slow speech/dysarthria/ speech disorder** (particularly with high doses or in long-term treatment, and are reversible), **headache, tremor, ataxia**

Uncommon: **emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia** (in the normal dose range, but especially at higher dose levels)

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

Uncommon: **diplopia** (particularly with high doses or in long-term treatment and is reversible)

Respiratory, thoracic and mediastinal disorders

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)** (see Sections 4.3 Contraindications and 4.4 Warnings and Precautions)

Gastrointestinal disorders

Common: **dry mouth, nausea, constipation**

Skin and subcutaneous tissue disorders

Uncommon: **rash**

Not known: **urticaria; Steven-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome);**

Musculoskeletal and connective tissue disorders

Not known: **muscle spasms, muscle weakness**

General disorders and administration site conditions

Very common: **fatigue**, especially at the beginning of treatment and when higher doses are used

Not known: **slow response to stimuli, hypothermia**

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.

Investigations

Uncommon: **weight increased** (particularly with high doses or in long-term treatment)

Injury poisoning and procedural complications

Uncommon: **fall**

Reporting of suspected adverse reactions:

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

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).

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.

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

Pharmacotherapeutic group: Benzodiazepine derivatives **ATC code:** N05BA09

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 (T_{max}) 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.

Biotransformation

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 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.

Other special populations

Elderly

Elderly persons are susceptible to lower clearance after oral administration. The terminal half-life is extended and the volume of distribution is increased. This can cause a greater clobazam accumulation after multiple administration than in younger people. Age also seems to affect the clearance and accumulation of active metabolite for elderly patients.

Hepatic Impairment

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

Renal Impairment

In patients with renal impairment, clobazam concentration in plasma decreases probably due to impaired absorption of the drug. The terminal half-life is largely not dependent on renal function.

5.3 Preclinical safety data

Chronic toxicity

In chronic toxicity studies in rats with daily oral clobazam administration of 12-1000 mg/kg, spontaneous activity was dose-dependently reduced, whereas respiratory depression and hypothermia were observed at the high dose level. Dose- dependent sedation, somnolence, ataxia and tremor were initially evident in dogs receiving daily oral doses of 2.5-80 mg/kg clobazam, which almost completely reversed in the course of the study. Similar dose-dependent effects were noted in monkeys after daily oral administration of 2.5-20 mg/kg.

Reproduction toxicity

In fertility studies in mice with daily administration of 200 mg/kg clobazam and in rats receiving daily doses of 85 mg/kg, no impairment of fertility and gravidity was observed.

Oral administration of clobazam to pregnant rats and rabbits throughout the period of organogenesis resulted in increased embryofetal mortality and increased incidences of fetal skeletal variations. In rabbits clobazam also decreased fetal body weights and increased the incidence of fetal malformations (visceral and skeletal). Additionally, oral administration of clobazam to rats throughout pregnancy and lactation resulted in decreased pup survival and alterations in offspring behaviour (locomotor activity). The observed embryo-fetal effects were associated with plasma exposures for clobazam and its major active metabolite N-desmethyloclobazam less than those in humans at the maximum recommended dose.

Genotoxicity and carcinogenicity

Clobazam is not genotoxic or tumorigenic. Follicular cell adenoma were significantly increased in rats at the 100 mg/kg clobazam high dose. In contrast to other species (mouse, dog, monkey), clobazam is known to activate the thyroid gland in rats like other benzodiazepine-containing agents. No effects on human thyroid function were noted at clinically relevant doses (20-80 mg).

A study in which clobazam (150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryo-fetal mortality and

incidences of fetal skeletal variations were increased at all doses. The low effect dose for developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and

desmethyloclobazam less than those in humans at the maximum recommended human dose of 60 mg/day. Oral administration of clobazam (10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryo-fetal mortality at the high dose. Incidences of fetal variations were increased at all doses.

The highest dose tested was associated with severe maternal toxicity (mortality). The low effect dose for embryo-fetal toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethyloclobazam less than those in humans at the maximum recommended human dose of 60 mg/day.

Additionally, oral administration of clobazam (50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryo-fetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behaviour (locomotor activity) at all doses.

The low effect dose for pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethyloclobazam less than those in humans at the maximum recommended human dose of 60 mg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

methyl parahydroxybenzoate (E218)

citric acid monohydrate (E330)

sodium citrate (E331)

sucralose (E955)

xanthan gum (E415)

purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

Discard 60 days after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle: Amber glass

Closure: HDPE-EPE wadded, tamper evident, child resistant screw on white plastic polypropylene cap.

Dosing Device: A 5ml polypropylene oral syringe with 0.1ml graduation mark and an adaptor for the syringe. Where higher doses are to be administered, dosing cups should be considered.

Pack size: 100ml and 150ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This product may settle during storage. Please shake the bottle thoroughly before use.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Syri Limited
Unit 4, Bradfield Road,
Ruislip, Middlesex
HA4 0NU, UK.

Trading as
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8 MARKETING AUTHORISATION NUMBER(S)

PL 39307/0073

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 December 2016
Renewal of the Authorisation: 27 January 2025

10 DATE OF REVISION OF THE TEXT

23/12/2025