SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Frisium® Tablets 10mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clobazam 10 mg.

3 PHARMACEUTICAL FORM

Tablet

Round, biconvex, white tablet, with score line on both face, one face engraved with C and 10 on the other side of the score line.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Frisium 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 Frisium 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, Frisium must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as Frisium) 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.

Frisium 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 60 mg 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 Treatment should always be withdrawn gradually.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 Frisium 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 5 mg daily. A maintenance dose of 0.3 – 1 mg/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 (see section 5.2). The 10 mg tablets can be divided into equal halves of 5 mg. 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

Frisium must not be used:

- In patients with hypersensitivity to benzodiazepines or any of the excipients of Frisium (see 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, see section 4.6).
- In breast-feeding women.

Benzodiazepines must not be given to children without careful assessment of the need for their use. Frisium 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 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.

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 clobazam. 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
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 (see 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 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, Frisium) 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 (see 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.

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 (see section 5.2).

Concomitant use of cannabidiol
The concomitant use of clobazam with cannabidiol-containing medicinal 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 clobazam 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 clobazam (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 clobazam, 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 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).

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% (see section 5.2) and therefore increase the effects of clobazam e.g. sedation (see section 4.5).

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.

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

Anticonvulsants
Addition of clobazam to established anticonvulsant medication (e.g. phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of Frisium 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 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 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.

CYP2D6 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

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 malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidence of cleft lip and palate were observed in 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 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 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 should not be given to breast-feeding mothers.

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

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 section 4.5).

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

The following CIOMS frequency rating is used, when applicable: *Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).*

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) (see section 4.4), agitation
Uncommon: abnormal behavior, 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) (see section 4.4), initial insomnia, anger, hallucination, psychotic disorder, poor sleep quality, suicidal ideation

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 is 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 section 4.3 and 4.4)

Gastrointestinal disorders
Common: dry mouth, nausea, constipation

Skin and subcutaneous tissue disorders
Uncommon: rash
Not known: photosensitivity reaction, urticaria, Stevens-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

Uncommon: weight increased (particularly with high doses or in long-term treatment, and is reversible)

Injury, poisoning and procedural complications
Uncommon: fall

Reporting of adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Teratogenicity
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-desmethylclobazam less than those in humans at the maximum recommended dose.

Impairment of fertility
A study in rats in which clobazam was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6 had no effect on fertility and early embryonic development. The study was limited as the highest dose was associated with plasma exposures for clobazam and N-desmethylclobazam less than those in humans at the maximum recommended dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, colloidal silicon dioxide, talc, magnesium stearate.

6.2 Incompatibilities

None

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister pack (Alufoil/PVC) containing 30 tablets

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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Basildon, Essex
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8 MARKETING AUTHORISATION NUMBER(S)

PL 43252/0052

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of latest renewal: 15 January 2002

10 DATE OF REVISION OF THE TEXT

08/07/2025