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

This package insert is continually updated. Please read carefully before using a new pack.

Clobazam Tablets IP

FRISIUM®,
FRISIUM® Jr.

COMPOSITION

Frisium® 5 mg
Each uncoated tablet contains
Clobazam I.P…. 5 mg
Excipients….q.s

Frisium® 10 mg
Each uncoated tablet contains
Clobazam I.P…. 10 mg
Excipients….q.s

Frisium® 20 mg
Each uncoated tablet contains
Clobazam I.P….20 mg
Excipients……q.s

Frisium® Jr.
Each film coated tablet contains
Clobazam I.P…. 5 mg ,
Colour: Titanium Dioxide I.P.
Excipients …….q.s

THERAPEUTIC INDICATIONS

- Acute and chronic anxiety states, which may produce the following symptoms in particular; anxiety, tension, restlessness, excitement, irritability, sleep disturbances from emotional causes, psychovegetative and psychosomatic disorders (for example, in the cardiovascular or gastrointestinal area), and emotional instability.

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

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

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

In cases of psychovegetative and psychosomatic disorders, the possibility of an organic cause is to be investigated.

- As adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant monotherapy.

DOSAGE AND ADMINISTRATION

Dosage
Dosage is generally based on the following guidelines:

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

Treatment of anxiety states
Adults and adolescents over 15 years of age: The initial dose is usually 20 mg clobazam daily. If necessary, the daily dose may be increased. Generally, it is recommended that a total daily dose of 30 mg is not exceeded

Elderly: Increased responsiveness and higher susceptibility to adverse effects may be present in elderly patients and require low initial doses and gradual dose increments under careful observation (see Precautions section). A maintenance dose of 10 to 15 mg clobazam daily is frequently sufficient

Children from 3 to 15 years of age: Increased responsiveness and higher susceptibility to adverse effects may be present in children and require low initial doses and gradual dose increments under careful observation. A daily dose of 5 to 10 mg clobazam is frequently sufficient. Benzodiazepines must not be given to children without careful assessment of the need for their use (see Contraindications section).

Secondary dosage adjustment: After improvement of the symptoms, the dose may be reduced

Timing of doses: If the dose is to be spread throughout the day, it is recommended that the larger portion be taken in the evening.

Duration of treatment: The duration of treatment must 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; treatment must not be extended without a 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.

Discontinuation of treatment: It is strongly recommended that after prolonged treatment clobazam is not withdrawn suddenly but rather that the dose is reduced gradually under medical supervision; otherwise withdrawal symptoms may occur (See Abuse and Dependence section)

Treatment of epilepsy in combination with one or more other anticonvulsants
Adults and adolescents over 15 years of age: It is recommended that administration be started at small doses (5 to 15 mg daily), if necessary, increasing the dose gradually to a maximum daily dose of about 80 mg.

Children from 3 to 15 years of age: It is recommended that normally treatment be started at 5 mg daily. A maintenance dose of 0.3 to 1.0 mg/kg body weight daily is usually sufficient. Higher susceptibility to adverse effects may be present in children and require gradual dose increments under careful observation; Benzodiazepines must not be given to children without careful assessment of the need for their use (see Contraindications section).

Elderly: Higher susceptibility to adverse effects may be present in elderly patients and require low initial doses and gradual dose increments under careful observation (see Precautions section)

Timing of doses: If the dose is spread throughout the day, it is recommended that the larger portion be taken in the evening. Doses of up to 30 mg clobazam can also be administered as a single evening dose.

Duration of treatment: 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.

Discontinuation of treatment: At the end of treatment - to include cases in which response to therapy has been poor - it is strongly recommended that clobazam is not withdrawn suddenly but rather that the dose is reduced gradually; otherwise an increased susceptibility to seizures as well as other withdrawal symptoms may occur.

SPECIAL POPULATIONS

Pediatric patients: see (Dosage & Administration; Contraindications section)

Elderly patients: see (Dosage & Administration; Precautions section)

Patients with renal or hepatic impairment: Increased responsiveness and higher susceptibility to adverse effects may be present in these patients and require low initial doses and gradual dose increments under careful observation (see Precautions section)

ADMINISTRATION

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

CONTRAINDICATIONS

Frisium®/ Frisium® Jr. must not be used

- in patients with hypersensitivity to clobazam or any of the excipients of Frisium® / Frisium® Jr.
- 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 impairment of liver function (risk of precipitating encephalopathy).
- 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**.**

WARNINGS

Alcohol

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

Risks from concomitant use of opioids and benzodiazepines

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

If a decision is made to prescribe 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 Interactions).

Amnesia

Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels.

Dependence

On withdrawal of benzodiazepines, especially if abrupt, a rebound phenomenon or a withdrawal syndrome may occur:

The rebound phenomenon is characterized by a recurrence in enhanced form of the symptoms which originally led to clobazam treatment (e.g. anxiety, seizures). This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness**.**

Once physical dependence has developed, abrupt termination of clobazam treatment will lead to withdrawal symptoms. These may include headaches, sleep disturbances, increased dreaming, extreme anxiety, tension, restlessness, confusion, and excitability, derealization, depersonalization, hallucinations and symptomatic psychoses (e.g. withdrawal delirium), numbness and tingling sensations in the extremities, muscle pain, tremor, sweating, nausea, vomiting, hyperacusis, hypersensitivity to light, noise and physical contact, as well as epileptic seizures.

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

In patients with a history of drug or alcohol dependence, there may be an increased risk of development of dependence with clobazam as with other benzodiazepines (see section Abuse and Dependence).

Pregnancy
There is limited amount of data for the use of clobazam in pregnant women. Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception. Clobazam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see section Pregnancy).

PRECAUTIONS

Serious Skin Reactions
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 Adverse Reactions).

Respiratory Depression
Clobazam can cause respiratory depression, especially if administered in high doses. Therefore, in patients with chronic or acute respiratory insufficiency, respiratory function must be monitored and a dose reduction may be necessary.

Clobazam is contraindicated in patients with severe respiratory insufficiency (see Contraindications section).

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

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 (see Dosage & Administration; Adverse Reactions section)

Tolerance in epilepsy
In the treatment of epilepsy with benzodiazepines - including Frisium / Frisium® Jr. consideration must be given to the possibility of a decrease in anticonvulsant efficacy (development of tolerance) in the course of treatment.

CYP2C19 poor metabolizers

In patients who are CYP2C19 poor metabolizers, levels of the active metabolite N-desmethylclobazam are expected to be increased as compared to extensive metabolizers. Dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration) (See section Pharmacokinetics)

Suicidality
Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with other benzodiazepines and hypnotics. There are very limited data available for clobazam in these studies. Cases of suicidal behavior have been reported with clobazam in post-marketing surveillance. All of these cases had confounding factors (see Indications and Adverse Reactions).

INTERACTIONS

Alcohol
Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% (See section Pharmacokinetics) and therefore lead to increased clobazam effects (see Warning section).

Central Nervous system depressant drugs
Especially when clobazam is administered in higher doses, a mutually potentiating effect is to be expected if other central nervous system depressant drugs (such as antipsychotics anxiolytics, certain antidepressant agents, anticonvulsant drugs, sedative antihistamines, anaesthetics, hypnotics or narcotic analgesics, or other sedatives) are taken at the same time. 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 Warnings).

Anticonvulsants
If clobazam is administered simultaneously with anticonvulsants in the treatment of epilepsy, the dosage must be adjusted under regular medical supervision (EEG monitoring), as there may be interactions with the patient's basic anticonvulsant medication.

In patients receiving concomitant treatment with valproic acid, there may be a slight to moderate rise in plasma valproic acid concentration.

Phenytoin plasma levels may rise if patients receive concomitant treatment with clobazam.

Where possible, it is recommended that blood levels of concomitantly administered valproic acid or phenytoin be monitored.

Carbamazepine and phenytoin 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 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 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.

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.

PREGNANCY
Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception. Clobazam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (See Warnings section)
Animal studies have demonstrated reproductive toxicity.

Clobazam crosses the placenta

In the post-marketing safety database, limited data on exposed pregnancies are available with clobazam.

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. However, in certain epidemiological case-control studies, an increased incidence of cleft lip and palate was observed with benzodiazepines.

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.

Administration of clobazam during the late phase of pregnancy or during childbirth can result in the occurrence of neonatal respiratory depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties (which may result in poor weight gain) in the newborn (signs and symptoms of the so-called "floppy infant syndrome").

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.

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

If a woman plans a pregnancy or becomes pregnant, carefully evaluate the risks and benefits and whether treatment with clobazam should be discontinued. If clobazam treatment is to be continued, use clobazam at the lowest effective dose.

LACTATION
Clobazam must not be used in breast-feeding women, since clobazam passes into breast milk.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
Some adverse effects (e.g., sedation, muscle weakness) may impair the patient's ability to concentrate and react, and, therefore constitute a risk in situations where these abilities are of special importance (e.g., operating a vehicle or machinery).

ADVERSE REACTIONS

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10%; Common ≥ 1 and < 10%; Uncommon ≥ 0.1 and < 1%;
Rare ≥ 0.01 and < 0.1%; Very rare < 0.01%; Not known (cannot be estimated from 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), 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), initial insomnia, anger, hallucination, psychotic disorder, poor quality sleep, 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 are reversible) ,headache, tremor, ataxia
Uncommon: emotional poverty, amnesia (may be associated with abnormal behavior), 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: Contraindications, Precautions)

Gastrointestinal disorders
Common: dry mouth, nausea, constipation

Skin and subcutaneous disorders
Uncommon: rash
Not known: urticaria, Steven-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome)

Musculoskeleteal 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.

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

Injury poisoning and procedural complications
Uncommon: fall

OVERDOSE

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

Management
In treatment for intoxication, it is recommended that the possible involvement of multiple agents be taken into consideration.

Gastric lavage, intravenous fluid replenishment and general supportive measures may be indicated in addition to monitoring of consciousness, respiration, pulse rate and blood pressure.

Facilities for the management of complications such as airways obstruction or respiratory insufficiency must be available.

Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathicomimetic agents.

Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective.

The efficacy of supplementary administration of physostigmine (a cholinergic agent) or of flumazenil (a benzodiazepine antagonist) cannot be assessed because insufficient experience is available.

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST
No information currently deemed necessary.

ABUSE AND DEPENDENCE
Benzodiazepines - including Frisium®/ Frisium® Jr. lead to physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment. However, this risk is present even with daily intake of clobazam over periods of only a few weeks, and applies not only to possible abuse with particularly high doses but also to the therapeutic dose range. The risk of dependence is increased in patients with a history of alcohol or drug abuse. The therapeutic benefit must be balanced against the risk of dependence during prolonged use.

On withdrawal of benzodiazepines, especially if abrupt, a rebound phenomenon or a withdrawal syndrome may occur (see also under Warnings section).

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

INCOMPATIBILITIES/ COMPATIBILITIES
Not applicable.

SHELF LIFE
See outer carton.

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