

Frisium® 10mg

clobazam

Tablets

1. NAME OF THE MEDICINAL PRODUCT

Frisium® 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Frisium® 10 mg:

Each tablet contains 10 mg Clobazam. Contains Lactose (see section 4.4).

For the full excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Frisium 10 mg, tablets:

Round, biconvex, white tablet with a scoreline on both faces, 7 mm in diameter

The tablets can be divided into equal doses of 5 mg.

4. CLINICAL PARTICULARS

4.1 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 cases of psychovegetative and psychosomatic disorders, the possibility of an organic cause must be investigated. In patients with depression or anxiety associated with depression, Frisium 10 must only be used in conjunction with adequate concomitant treatment, since the use of benzodiazepines (e.g. Frisium 10) alone can precipitate suicide. 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.
- As adjunctive therapy in patients with epilepsy not adequately stabilised with their basic medication.

4.2 Posology and method of administration

Dosage

The pharmaceutical form, dosage and duration of use must be adapted to the response of the individual, the therapeutic indication and the severity of the disease. It is important to watch for possible impairment of reactions. The principle of keeping the dose as low as possible applies.

Treatment of anxiety:

In general, the starting dose is 20 mg of clobazam per day. The daily dose can be increased to 30 mg of clobazam if required.

Elderly patients

As elderly patients may react more strongly to treatment with Frisium and may be more prone to undesirable effects, it is necessary to start with a low dose and increase it gradually under careful observation (see section 4.4).

A daily dose of 10-15 mg of clobazam is often sufficient for elderly patients.

Withdrawal of treatment for anxiety:

Once the symptoms have improved, the dose can be reduced. Frisium should not be withdrawn suddenly after prolonged use. The dose should be reduced gradually under medical supervision, otherwise symptoms such as restlessness, anxiety and insomnia may recur.

Combination with an anti-epileptic or several other anti-epileptics for treatment of epilepsy:

In common with other benzodiazepines, the anti-epileptic efficacy of Frisium may decline over the course of the treatment.

Adults

A starting dose of 5-15 mg of clobazam per day is increased gradually to a maximum daily dose of approx. 80 mg of clobazam. Constant doses (e.g. 20 mg/day) and intermittent treatment (temporarily withdrawing and then rescribing Frisium) have also proved effective.

Children from 6 years of age

It is recommended to start treatment of clobazam at 5 mg daily. A maintenance dose of 0.3 to 1.0 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 for children under 6 years of age.

Elderly patients

Higher susceptibility to adverse effects may be present in elderly patients and require low initial doses and gradual dose increments under careful observation (see section 4.4).

Withdrawal of combination treatment for epilepsy:

Even if it has been unsuccessful, the treatment should be withdrawn by reducing the dose gradually, otherwise an increased tendency to seizures cannot be ruled out.

Patients with impaired hepatic and renal function:

As patients with impaired hepatic and renal function may react more strongly to treatment with Frisium and may be more prone to undesirable effects, it is necessary to start with a low dose and increase it gradually under careful observation. In the event of long-term treatment, hepatic and renal function should be monitored as a precaution.

Method of administration

The tablets can be administered whole, or crushed and mixed in apple purée. Frisium 10 mg tablets can be divided into equal doses of 5 mg. Frisium can be given with or without food. If the dose is spread out over the day, a higher proportion should be taken in the evening. Doses of up to 30 mg of clobazam may also be prescribed as a single evening dose.

If stress-related sleep disturbances predominate, a single evening dose is recommended.

Duration of administration

In cases involving acute states of tension, agitation and anxiety, the use of Frisium should be confined to single doses or a few days.

In cases involving chronic states of tension, agitation and anxiety, the duration of use depends on the course of the disorder. The doctor should assess the condition of the patient no more than two weeks after the start of treatment and regularly thereafter in order to decide whether the treatment should be continued, especially if the patient is free of symptoms.

In general, the total duration of treatment should not exceed 8-12 weeks (including the period in which the dose is reduced). In certain cases, it may be necessary to extend the maximum treatment period. In such cases, the treatment should not be extended without reassessing the condition of the patient. Continuous long-term use should be avoided because it can lead to dependence.

In cases involving combination treatment for epilepsy, the doctor should assess the condition of the patient no more than four weeks after the start of treatment and regularly thereafter in order to decide whether the treatment should be continued. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose.

At the end of treatment (including 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 any of the following circumstances:

- Hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1,
- Myasthenia gravis,
- Severe respiratory insufficiency,
- Sleep apnoea syndrome,
- Severe liver dysfunction,
- Acute intoxication with alcohol or other centrally acting substances,
- History of dependence on alcohol, medicinal products or drugs,
- Lactation.

4.4 Special warnings and precautions for use

In patients with schizophrenia or other psychoses, benzodiazepines are recommended only as an additional medicinal product, i.e. not as the primary form of treatment.

In patients with depression or anxiety linked to depression, Frisium may only be used in combination with an appropriate concomitant medicinal product.

Not all states of tension, agitation and anxiety require treatment with a medicinal product. They are often a manifestation of physical or mental illness and can be influenced by other measures or treatment of the underlying disease.

Frisium may only be taken if prescribed by a doctor and under constant medical supervision. It is irresponsible to pass medicinal products prescribed for personal use on to others.

Alcohol

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

Risks from concomitant use of opioids and benzodiazepines

Concomitant use of benzodiazepines, including clobazam, and opioids 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 4.5).

Amnesia

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

Dependence

As with other medicinal products containing benzodiazepines, administration should only be continued if absolutely essential and after careful evaluation of the therapeutic benefit against the risk of habituation and dependence.

All benzodiazepines can lead to physical and psychological dependence, the risk of which increases with the dose and duration of treatment. Even daily administration for a few weeks puts the patient at risk of developing dependence. This applies not only to the misuse of high doses but also to the therapeutic dose range. Patients with a known history of alcohol or medicinal product abuse have a higher risk of developing dependence.

Rebound phenomena/withdrawal symptoms

A rebound phenomenon or withdrawal syndrome can occur, especially if benzodiazepines are withdrawn suddenly. For this reason, the treatment should end with a gradual reduction in the dose.

The reappearance of symptoms that originally led to treatment with Frisium in an intensified form (e.g. states of anxiety, epileptic seizures) is characteristic of a rebound phenomenon. This may be accompanied by reactions such as mood swings, sleep disturbances and restlessness.

Once physical dependence has developed, sudden withdrawal of treatment with Frisium leads to withdrawal symptoms. Such symptoms include headache, muscle pain, sleep disturbances, increased

dreaming, anxiety, states of tension, restlessness, confusion and agitation, tremor, sweating, symptomatic psychoses (e.g. withdrawal delirium) and epileptic seizures.

A withdrawal syndrome can also occur if treatment switches suddenly from a long-acting benzodiazepine (e.g. Frisium) to one with a short duration of action.

When Frisium is withdrawn after a prolonged period of use (more than a week), the dose should be reduced gradually. Consideration should be given to the possibility of temporary withdrawal phenomena. Abrupt withdrawal may provoke convulsions, especially if the medicinal product has been used as an anticonvulsant.

Development of tolerance

Patients should be expected to develop tolerance if Frisium is used as an anticonvulsant for several months.

Paradoxical reactions

During the use of benzodiazepines the occurrence of paradoxical reactions such as restlessness, irritability, aggression, delusion, anger, nightmares, hallucinations, psychotic disorders, agitation, sleep disturbances, suicidal ideation, increased muscle spasms and anxiety has been reported. Such reactions are to be especially expected in children and elderly people. If paradoxical reactions occur, treatment with clobazam should be discontinued.

Suicidal ideation/suicide attempts/suicide and depression

Several epidemiological studies indicate a greater incidence of suicidal ideations, suicide attempts and suicide in patients with or without depression who were treated with benzodiazepines or other hypnotics, including clobazam. However, no causal link has been proven (see section 4.8).

Therefore, patients should be monitored and a suitable treatment considered with respect to signs of suicidal thoughts and suicidal behaviour patterns. Patients (and their carers) should be advised to obtain medical help if signs of suicidal thoughts or suicidal behaviour occur.

Serious skin reactions

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with Frisium in both children and adults during post-marketing surveillance. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs, that are associated with serious skin reactions.

SJS and 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. In this case clobazam must no longer be used and alternative therapeutic options should be considered.

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. Dosage adjustment of clobazam may be necessary (e.g. low starting dose with careful dose titration).

Concomitant use with cannabidiol

The concurrent use of clobazam with medicinal and non-medicinal products containing cannabidiol can increase levels of n-desmethyloclobazam, which leads to an increased incidence of drowsiness and sedation. It may be necessary to adjust the dose of clobazam. Non-medicinal products containing cannabidiol must not be used in combination with clobazam since they contain unknown quantities of cannabidiol and differ in terms of quality (see sections 4.5 and 5.2).

High-risk patients

At the start of treatment, the treating doctor should monitor the individual response of the patient to the medicinal product in order to detect any relative overdoses as quickly as possible. This applies particularly to children, elderly patients and patients in poor general condition as well as to patients with organic brain changes, circulatory failure or respiratory failure. Patients should also be given specific instructions for everyday life, taking into account their specific situation (e.g. occupation).

Patients with renal and hepatic impairment

In patients with impairment of renal or hepatic function, responsiveness to Frisium (intensified and prolonged effect) and susceptibility to adverse effects might be increased and therefore dose reduction might be necessary. In long-term treatment renal and hepatic function must be checked regularly.

Elderly patients

In elderly patients there might be an increased sensitivity to adverse reactions such as drowsiness, dizziness and muscle weakness. Therefore, a dose reduction is recommended (see section 4.2 and 4.8). Care should be taken in elderly patients especially when getting up at night due to risk of fall.

Children

Benzodiazepines must not be given to children without careful assessment of the need for their use (see section 4.2).

Respiratory depression

Clobazam can cause respiratory depression, especially if administered at 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 section 4.3).

Muscle weakness

Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia, Frisium should only be used with particular caution and if necessary with reduced dose. Clobazam is contraindicated in patients with myasthenia gravis (see section 4.3).

Long-term treatment

As a precaution, hepatic and renal function should be monitored during long-term treatment.

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

This is a medicament

- Medicament is a product which affects your health, and this consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Please note the following information for the patient:

This preparation contains a "benzodiazepine". Benzodiazepines are medicines for the treatment of, e.g., certain disorders which are associated with restlessness and anxiety states, inner tension or insomnia. When using benzodiazepines, there is a risk of developing or furthering dependence.

To minimise this risk, please follow strictly these instructions:

1. Benzodiazepines have been developed solely for the treatment of a specific group of illnesses and may only be taken on your doctor's instructions.
2. When these medicines have been taken for a maximum of four weeks, the doctor should decide whether to continue the treatment. An uninterrupted, prolonged period of administration should be avoided, as it may lead to dependence. If you take these drugs without consulting your doctor, you will reduce your chances of benefiting from them.
3. On no account increase the dose prescribed by your doctor, even if the effect has weakened. Treatment will not have the desired effect if you increase the dose on your own.
4. When benzodiazepines are discontinued after prolonged use, restlessness, anxiety states, and insomnia may occur, often after a delay of several days. These withdrawal symptoms usually disappear after 2–3 weeks.
5. Tell your doctor if you have suffered or are still suffering from alcohol or drug dependence. If this is the case, you must not take benzodiazepines, except in rare situations determined only by the doctor.
6. Never take benzodiazepine-containing medicines because "they have been such a help to someone else", and do not pass these preparations on to others.
7. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose-malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Central nervous system depressant drugs/alcohol

If other medicinal products with a depressant effect on the central nervous system (e.g. neuroleptics, tranquillisers, antidepressants, hypnotics/sedatives, anaesthetics, beta blockers, opiate analgesics, sedative antihistamines, antiepileptics) are taken at the same time as high doses of Frisium in particular, each is likely to intensify the effect of the other. This applies particularly to concomitant alcohol consumption, which can alter or intensify the effects in an unpredictable way. Alcohol can increase the bioavailability of clobazam by 50%, thereby intensifying the effect of Frisium. For this reason, the patient should refrain from drinking alcohol during treatment with Frisium.

Opioids

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

MAO inhibitors

If medicinal products that inhibit the monoxygenase system, such as cimetidine and erythromycin, are taken concurrently, the effect of Frisium may be intensified and prolonged.

Anticonvulsants

If anti-epileptics are also being taken simultaneously for seizures, the adjustment phase of the treatment must be conducted under medical supervision (EEG monitoring), as the medicinal product may interact with the anti-epileptic basic treatment.

Concomitant administration of valproic acid and Frisium may result in a slight to moderate increase in the plasma concentration of valproic acid. Blood levels of phenytoin may rise if patients are treated with Frisium simultaneously. If possible, blood levels of valproic acid and phenytoin should be determined in such cases.

Carbamazepine and phenytoin can lead to an increase in the biotransformation of clobazam into the active metabolite N-desmethyclobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethyclobazam through inhibition of CYP3A4 and CYP2C19. Monitoring of blood levels is recommended prior to initiation of stiripentol and then once a 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/nitrous oxide

With concomitant use of muscle relaxants the muscle relaxing effect may be enhanced, especially in elderly patients and in case of higher dosage (risk of fall).

The effect of nitrous oxide may be enhanced.

CYP2C19 inhibitors

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethyclobazam (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

Concurrent administration of cannabidiol and clobazam produces bidirectional pharmacokinetic interactions. Data from a study of healthy volunteer subjects indicates that concurrent use with cannabidiol increases levels (3 to 4 times) of N-desmethyclobazam (an active metabolite of clobazam), probably as a result of CYP2C19 inhibition. Increased systemic levels of these active substances can lead to stronger pharmacological effects and an increase in undesirable drug effects. Concurrent use of cannabidiol and clobazam increases the incidence of drowsiness and sedation. A reduction of the clobazam dose should be considered if drowsiness or sedation occur when clobazam is used concomitantly 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 is only a limited amount of data from the use of clobazam in pregnant women. Nevertheless, far-reaching experience documented in cohort studies has not yielded evidence of severe fetal malformations with the use of benzodiazepines in the first trimester of pregnancy, although some specific case control studies revealed cases of cleft lip and cleft palate.

Clobazam is not recommended during pregnancy or 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 about the benefits and risks of using clobazam during pregnancy and should be instructed to contact their doctor about discontinuing clobazam if they become pregnant or plan to become pregnant. If treatment with clobazam is continued, the lowest effective dose should be used.

Cases of reduced fetal movement and variability in fetal heart rate have been described with the use of benzodiazepines during the second and third trimesters of pregnancy.

If clobazam is administered during the later stages of pregnancy or during childbirth, effects may occur in the newborn, such as respiratory depression (including respiratory distress and apnoea), signs of sedation, hypothermia, hypotonia and feeding difficulties (floppy infant syndrome).

Additionally, the children of mothers who used benzodiazepines long-term in the later stages of pregnancy may develop a physical dependency, thus creating a risk of withdrawal symptoms after birth. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breast-feeding

Frisium must not be taken during lactation because the active substance clobazam passes into breast milk. If treatment is absolutely essential, the infant should be weaned.

Fertility

No disturbance of fertility was observed in fertility studies in animals (see section 5.3). However, exposure in animals was less than after the maximum recommended therapeutic dose.

4.7 Effects on ability to drive and use machines

Even if used as instructed, this medicinal product may affect reactions to such an extent that the ability to drive or use machines is impaired. This applies particularly in combination with alcohol.

Therefore, patients should refrain from driving, using machines or undertaking any other hazardous activities entirely, or at least for the first few days of treatment. The decision in each individual case is made by the treating doctor, taking into account the response of the patient and the dose concerned.

4.8 Undesirable effects

Undesirable effects are ranked by frequency, using the following convention:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1\,000$ to $< 1/100$)

Rare ($\geq 1/10\,000$ 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 (in patients with a pre-existing depressive disorder, depressive moods may be aggravated), drug tolerance (especially during prolonged use), agitation.

Uncommon: abnormal behaviour, confusional state, anxiety, delusion, nightmares, loss of libido (reversible; occurs particularly with high doses or long-term treatment).

Frequency not known: dependence (particularly in cases of prolonged use; see section 4.4), 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, impaired attention, slow speech/dysarthria/speech disorder (reversible; occurs particularly with high doses or long-term treatment), headache, tremor, ataxia.

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

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

Eye disorders

Uncommon: diplopia (reversible; particularly with high doses or long-term treatment).

Respiratory, thoracic and mediastinal disorders

Frequency not known: respiratory depression, respiratory failure (may develop or worsen particularly in patients with pre-existing compromised respiratory function, e.g. in patients with asthma, or in patients with brain damage) (see sections 4.3 and 4.4).

Gastrointestinal disorders

Common: dry mouth, constipation, nausea.

Skin and subcutaneous tissue disorders

Uncommon: rash. *Frequency not known:* urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome).

Musculoskeletal and connective tissue disorders

Frequency not known: muscle spasms, muscle weakness.

General disorders

Very common: fatigue (especially at the beginning of treatment and when higher doses are used).

Frequency not known: slow response to stimuli, hypothermia.

Investigations

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

Injury

Uncommon: risk of fall (risk of severe injuries) (see section 4.4).

4.9 Overdose

a) Symptoms of intoxication

Overdose and intoxication with Frisium and other benzodiazepines can cause depression of the central nervous system with the following symptoms: drowsiness, confusion and somnolence. The condition can progress to ataxia, respiratory depression, a drop in blood pressure and, in rare cases, coma. The symptoms of an overdose are more pronounced and may be life-threatening if other substances that affect the brain, including alcohol, are taken simultaneously.

Previous reports of overdose in the literature involving ingestion of up to ten times the recommended therapeutic daily dose did not result in any clinically significant damage. Symptoms included interruption of sleep by auditory stimuli or drowsiness and clouding of consciousness as well as weakness in the legs lasting a day.

Most cases of severe acute intoxication reported to the manufacturer involving Frisium have been of combined intoxication with other psychotropic drugs or hypnotics.

Three cases of overdose have been caused largely by Frisium itself. In two of these cases, the dose is unknown but serum levels of clobazam peaked at 2.8 and 1.5 mg/ml. In the third case, 880 mg was taken.

These three cases all resulted in a sleep-like or comatose state lasting 8 to 24 days. One patient did not react to pain stimuli for the first 5 days. In all cases, spontaneous breathing was unaffected.

b) Treatment of intoxication

In addition to monitoring respiration, pulse and blood pressure, gastric lavage, intravenous fluid replacement and general supportive measures are indicated.

Facilities for dealing with complications such as obstruction of the airways or respiratory failure must be available.

Hypotension can be treated with plasma replacement and, if necessary, sympathomimetics.

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

There is insufficient experience of additional administration of cholinergic physostigmine or the benzodiazepine antagonist flumazenil for an assessment of efficacy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytic (tranquiliser) and anticonvulsant, 1,5-benzodiazepine

ATC-code: N05BA09

Tranquilising effect

Experimental models with various animal species have shown clobazam to have a clearly pronounced tranquilising, anxiolytic and aggression-reducing effect. At therapeutically relevant doses, the tranquilising effect occurs without impairing motor activity.

Effect on motor coordination

Like all benzodiazepines, clobazam influences muscle coordination. However, it differs from other substances, e.g. diazepam and chlordiazepoxide, in that the impairment is much less severe.

Anticonvulsant effect

Various animal models have shown clobazam to have a pronounced anticonvulsant effect exceeding that of chlordiazepoxide.

Potentiation of anaesthesia and analgesic effect

Clobazam prolongs anaesthesia after administration of various barbiturates in mice. The narcotic effect of alcohol is also intensified by clobazam.

Clobazam was also found to have an analgesic effect in three different pain tests.

Cardiovascular effect

The effect of clobazam on the cardiovascular system has been tested in various animal species. A minimal effect, largely in the form of a slight decrease in blood pressure, pulse and respiratory rate, was only evident after a dose 20 to 200 times higher than the corresponding human dose.

5.2 Pharmacokinetic properties

Clobazam is virtually insoluble in water (1:12 500) and its apparent coefficient of distribution is 9 (n-octanol/phosphate buffer pH 7.4).

Absorption

After oral administration, clobazam is rapidly and extensively absorbed. Administration of clobazam as capsules, tablets or solution (in propylene glycol) had no significant effect on its relative bioavailability. Time to peak plasma concentrations (t_{max}) is achieved after 0.5–4.0 hrs.

The administration of clobazam tablets with food or crushed in apple purée slows the rate of absorption by approximately one hour but does not affect the overall extent of absorption. Clobazam can be given without regard to meals.

Concurrent alcohol consumption can increase bioavailability of clobazam by 50%.

Distribution

After a single dose of 20 mg of 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 independent of concentration within the therapeutic range. Approximately 80-90% of clobazam is bound to plasma proteins, whereas binding to cellular blood components is minimal.

Following twice-daily administration, clobazam accumulates approximately 2-3 times the steady-state while the active metabolite N-desmethyclobazam (N-CLB) accumulates approximately 20 times. The steady-state concentration is reached within approximately 2 weeks.

Biotransformation

Clobazam is rapidly and extensively metabolised in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethyclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main metabolite found in human plasma. N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-N-desmethyclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolisers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolisers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan leads to increases of 90% in AUC and 59% in C_{max} values for dextromethorphan.

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 is excreted through the kidneys.

Clobazam crosses the placental barrier and can also be detected in breast milk. Active clobazam concentrations can be reached in fetal blood and breast milk.

5.3 Preclinical safety data

Repeated dose toxicity

Repeated dose toxicity studies in rats showed a dose-dependent reduction in spontaneous activity after an oral daily dose of 12-1 000 mg of clobazam per kg. A decrease in weight gain, respiratory depression and hypothermia were seen at the highest dose.

Studies in dogs initially showed dose-dependent sedation, somnolence, ataxia and slight tremor after a daily dose of 2.5-80 mg/kg. Later, these symptoms almost completely disappeared. Similar dose-dependent effects were observed in monkeys after an oral daily dose of 2.5-20 mg/kg of clobazam.

Reproductive toxicity

Clobazam did not impair fertility in mice at doses of 200 mg/kg daily and in rats at doses of 85 mg/kg daily. Also, in another fertility study, the fertility of male and female rats was not impaired up to the maximum oral dose of 750 mg/kg/day.

In studies concerning embryo-fetal development, an increase of fetal mortality and developmental delay of the fetus with respect to skeletal variations was observed in rats at oral doses of 150-750 mg/kg/day.

In rabbits, oral doses over 30 mg/kg/day resulted in decreased fetal body weights and increased visceral and skeletal malformations of the fetus. Oral administration of the highest dose of 75 mg/kg/day additionally resulted in increased fetal mortality, presumably due to maternal toxicity.

In a study concerning pre- and postnatal development in rats, pup survival was decreased at oral doses over 350 mg/kg/day. Additionally, the young animals showed increased motor activity at all doses (≥ 50 mg/kg/day).

In all these studies, the plasma exposures of rats and rabbits for clobazam and N-desmethyclobazam (AUC) were lower than those of humans at the maximum recommended human dose of 80 mg/kg/day.

Carcinogenic and mutagenic potential

A significant increase in the incidence of follicular cell adenoma was found in rats in the highest dose group (100 mg/kg of body weight). It is known that clobazam, like other benzodiazepines, leads to activation of the thyroid in rats. These changes have not been observed in studies of other species (mice, dogs and monkeys). Clobazam is not genotoxic and does not transform cells. No effects on thyroid function have been observed in humans at the clinically relevant dose range (20-80 mg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Frisium 10 mg:

Lactose monohydrate, maize starch, Silica, colloidal anhydrous, talc, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use later than the date of expiry.

Keep medicines out of the reach of children.

6.4 Special precautions for storage:

Do not store above 30°C.

6.5 Nature and contents of container:

100 tablets

7. MANUFACTURER

DELPHARM DIJON

6 boulevard de l'Europe,

21800 Quetigny, France

8. DATE OF REVISION

Oct 2022

(CCDS v6, v7 and v8.1 (based on DE SmPC dated Nov 2020))