Frisium® 10mg

Clobazam

[sanofi logo]

Tablets

Composition
Each tablet contains 10mg clobazam as active ingredient.
Excipients: Lactose, maize starch, colloidal anhydrous silica, talc, magnesium stearate.

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 gastro-intestinal area), and emotional instability.
In cases of psychovegetative and psychosomatic disorders, the doctor should investigate the possibility of an organic cause.
Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjuvant of different treatment.
- As adjunctive therapy in patients with epilepsy who are not adequately stabilized with their anticonvulsant mono-therapy.

Contraindications
Frisium10 must not be used
- In patients with hypersensitivity to clobazam or any of the excipients, or with any history of drug dependence.
- In patients with myasthenia gravis (risk of aggrevation 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
- During the first trimester of pregnancy(for use during second and third trimester, see section Fertility, Pregnancy and Lactation)
- Benzodiazepines must not be given to children without careful assessment of the need for their use.

Children between the ages of 6 months and 3 years should not normally be given Frisium10; however, in exceptional cases, where there are compelling indications, it can be used for anticonvulsant treatment.

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, Frisium10 must 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.

Frisium10 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 clobazam (increased risk of sedation and other adverse effects).

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.

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.

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

The rebound phenomenon is characterized by a reappearance of symptoms that originally led to treatment with Frisium10 in an intensified form (e.g. states of anxiety, epileptic seizures). This may be accompanied by reactions such as mood swings, sleep disturbances and restlessness.

Once physical dependence has developed, sudden withdrawal of treatment with Frisium10 leads to withdrawal symptoms. Such symptoms include headache, muscle pain, sleep disturbances, increased dreaming, anxiety, states of tension, restlessness, confusion and agitation, derealisation, 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 if treatment switches suddenly from a long-acting benzodiazepine (e.g. Frisium) 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.

Pregnancy
There are limited amount of data from the use of clobazam in pregnant women. Clobazam is contraindicated during the first trimester of pregnancy and not recommended 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.

Development of tolerance
Patients should be expected to develop tolerance if Frisium10 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, nightmare, hallucination, psychotic disorder, agitation, sleep disturbances, suicidal ideation, frequent muscle spasms and anxiety has occasionally 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 thoughts and suicidal behaviour

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.

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.

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.

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).

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 told exactly how to behave in 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 clobazam (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 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.

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

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

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.

Muscle weakness
Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia, Frisium10 should only be used with particular caution and if necessary with reduced dose, Clobazam is contraindicated in patients with myasthenia gravis.

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

Fertility, pregnancy and lactation
Pregnancy

There is only a limited amount of data from the use of clobazam in pregnant women. Some of the cases reported fetal malformations, but maternal epilepsy or coadministration of antiepileptic medications were confounding factors. Animal studies have demonstrated reproductive toxicity.

As a precautionary measure, Frisium must not be used during the first trimester of pregnancy unless the clinical condition of the woman requires treatment of the epilepsy with clobazam. Clobazam is not recommended in women of childbearing potential not using contraception.

If Frisium is prescribed to a woman of childbearing potential, the patient should be informed about the benefit and risks of the use of clobazam during pregnancy and should be instructed to immediately inform her physician if she is planning to become pregnant or thinks she might be pregnant. Then it should be considered and decided whether treatment with Frisium should be discontinued or continued with the lowest effective dose.

If administration of Frisium during the later stages of pregnancy or during childbirth is indicated due to compelling medical reasons, respiratory depression (including respiratory distress and apnoe) may occur in the newborn because of its pharmacological effect. This may be associated with other disorders such as sedation signs, hypothermia, hypotonia and feeding difficulties (so called ‘floppy infant syndrome’).

Prolonged use of Frisium in the later stages of pregnancy can lead to habituation and dependence in the infant and a withdrawal syndrome in the newborn. Appropriate monitoring of the newborn in the postnatal period is recommended.

Lactation
Frisium10 must not be used in breast-feeding women, since clobazam passes into breast milk.

Fertility
No disturbance of fertility was observed in fertility studies in animals

Adverse reactions
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)

Gastrointestinal disorders
Common: dry mouth, nausea, constipation

Skin and subcutaneous disorders
Uncommon: rash
Not known: photosensitivity reaction 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

Interactions
Central nervous system depressant drugs/alcohol
Especially when Frisium10 is applied 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. 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 Frisium10.

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

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

Anticonvulsants
If Frisium10 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, especially in patients receiving concurrent treatment with valporic acid and valporic acid concentrations. Phenytoin plasma levels may rise if patients receive concomitant treatment with clobazam. If possible, the blood levels of the active ingredients should be determined in such cases. Carbamazepine and phenytoin may cause an increase in the metabolic conversion of clobazam to N-des-methyl 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 analgesis
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 2 D6 substrates
Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol) may be necessary.

Dosage
Pharmaceutical presentation, dosage, and duration of treatment must be adjusted to the individual clinical response, the indication, and the severity of the condition. 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.
When treatment with Frisium10 is to be discontinued after prolonged administration, the dosage should normally be tapered off over a period of time.

Treatment of anxiety states:
Adults and adolescents over 15 years of age: The initial dose is usually 20mg Frisium10 daily. If necessary, the daily dose may be increase to 30mg. 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. A total daily dose of 10-15mg is often enough.

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 5-10 mg is frequently sufficient. Benzodiazepines must not be given to children without careful assessment of the need for their use.

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*:* After improvement of the symptoms, the dose may be reduced. After prolonged treatment, Frisium10 should not be withdrawn suddenly. The dose should be reduced gradually under medical supervision, otherwise symptoms such as restlessness, anxiety, and insomnia may occur.

T*reatment of epilepsy in combination with one or more other antiepileptics:*
Adults and adolescents over 15 years of age: Small doses (5-15mg/day as the initial dose), gradually increasing to a maximum daily dose of about 80mg. Furthermore, constant doses (e.g. 20mg/day) and intermitted therapy (discontinuing Frisium10 and subsequently prescribing it again) have proven effective.

Children from 3 to 15 years of age: Treatment should normally be started with 5mg, and a maintenance dose of 0.3-1.0 mg/kg body weight daily is usually enough. 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.

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

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 oftreatment: At the end of treatment – also in cases where there has been a poor response to therapy – the dose should be gradually reduced, because otherwise and increased proneness to seizures as well as other withdrawal symptoms cannot be excluded.

Administration

The tablets should not be swallowed whole with some liquid. If the dose is to be distributed over the day, the larger portion should be taken in the evening. Doses of up to 30mg Frisium10 can also be administered as a single evening dose.

The duration of treatment is determined by the doctors. After a period not exceeding 4 weeks, the doctor should decide whether continuation of treatment is necessary. Prolonged spells of uninterrupted treatment should be avoided, since they may lead to dependence.

Overdose

Symptoms of intoxication

Overdose and intoxication with Frisium10 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 have involved a combination of Frisium10 and other psychotropic drugs or hypnotics.

Three cases of overdose have been caused largely by Frisium10 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.

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 of the active substance (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.

Pharmacodynamics properties
Clobazam is an anxiolytic and anticonvulsant of the benzodiazepine group.

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 prolonged 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.

Pharmacokinetics 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. Relative bioavailability of clobazam capsules, tablets or solution (in propylene glycol) was not significantly different.
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 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 hours71. 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.72
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.

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 feces. Less than 1 % of unchanged clobazam and less than 10% of unchanged N-CLB are excreted through the kidneys.

Expiry date
Do not use later than the date of expiry

Keep medicines out of the reach of children

Special precautions for storage:
Do not store above 30°C

Presentation
10, 20 and 100 tablets. Not all pack size maybe marketed.
Hospital packs

Holder/ Distributor
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

Manufacturer
Sanofi Winthrop Industrie
56, route de Choisy au Bac
60205 Compiĕgn, France

Date of last revision
July 2018

Please note the following information for the patient:
This preparation contains a "benzodiazepine".
Benzodiazepines are drugs for the treatment of certain diseases which are associated with restlessness and anxiety states, inner tension or insomnia. When using benzodiazepines, there is a risk of developing or promoting dependence, to minimize this risk, you are advised to observe the following instructions exactly:

1. Benzodiazepines have been developed solely for the treatment of a specific group of illnesses, and may only be taken on doctor's instructions.

2. When these drugs have been taken for a maximum of four weeks, the doctor should decide whether the treatment is to be continued. An uninterrupted, prolonged period of administration should be avoided, as it may lead to dependence. If these drugs are taken without consulting the doctor, the chance of them helping you is reduced.

3. On no account increase the dose prescribed by the doctor, even if the effect has lessened. Treatment will not have the desired effect if you increase the dose on your own initiative.

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, or hard drug addiction. If this is the case, you must not take benzodiazepines, except in rare situations determined only by the doctor.

6. Never take benzodiazepine-containing drugs because “they have been such a help to someone else”, and do not pass the preparations on to others.