

Data Sheet

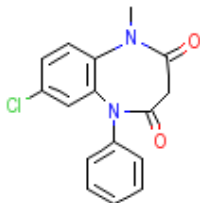
Frisium[®]

Name of Medicine

Non-proprietary Name

Clobazam

Chemical Structure



CAS Number

22316-47-8

Description

Clobazam is the first anxiolytic drug which belongs to the class of 1,5 rather than 1,4-benzodiazepines. Clobazam differs from the 1,4-benzodiazepines in that the nitrogen atoms in the 7-membered heterocyclic ring are located at positions 1 and 5 and an oxo substituent is located at position 4. This chemical difference confers both chemical and pharmacological properties upon clobazam which distinguish it from diazepam and other compounds of the 1,4-benzodiazepine series.

Pharmacology

Class

Clobazam is an anxiolytic and anticonvulsant of the benzodiazepine group.

Site and Mode of Action

Electrophysiological investigations have shown that the most important sites of action of the benzodiazepines are the limbic system, the thalamus and the spinal cord. At the synaptic level it has been proposed that various neurological systems including those utilising noradrenaline, dopamine, serotonin, acetylcholine, glycine and gamma-aminobutyric acid (GABA) as neurotransmitters may be involved in the mediation of the pharmacological effects.

Pharmacodynamics

Evidence suggests that the observed decreased turnover rate of these various neurotransmitters can be explained in a unified way by a primary action of benzodiazepines on the GABA system through a facilitation of GABA-ergic neurotransmission. GABA is the major inhibitory neurotransmitter in the mammalian brain. In most brain regions GABA is the transmitter of postsynaptic inhibitions, but at certain brain stem synapses GABA mediates presynaptic inhibition. Benzodiazepines may enhance both of these actions of GABA.

Recent studies have demonstrated the presence of specific binding sites for benzodiazepines which are independent of GABA sites which occur exclusively in the central nervous system.

The concentration of the binding sites is highest in the cerebral and cerebellar cortex followed by areas of the limbic system, the basal ganglia and the brain stem. It remains to be demonstrated

whether benzodiazepine receptors are associated with GABA synapses or whether they show a wider pattern of distribution.

Like the 1,4-benzodiazepines, Frisium has been found to be an effective anti-anxiety agent and produces approximately equivalent anxiolytic activity compared to diazepam when used on a 2:1 dosage basis (Frisium: diazepam). Frisium produces almost no muscular relaxation at normal dosage levels.

Pharmacokinetics

Absorption

Clobazam is rapidly and completely absorbed from the gastrointestinal tract with peak plasma levels being achieved within two hours. The presence of food delays but does not affect the extent of absorption.

Distribution

Peak serum concentrations of clobazam occurred between one and four hours after oral administration, irrespective of the dose given. After a single 10 mg dose the peak serum concentration was found to be approximately 200 nanogram/mL. There are large differences between individuals in the levels reached. Approximately 85% of clobazam is bound to plasma proteins in the concentration range 50-10,000 nanogram/mL.

Metabolism

Clobazam is metabolised by demethylation, hydroxylation and methoxylation. Following oral administration the serum contains unchanged clobazam with the chief metabolite being N-desmethyl-clobazam and smaller amounts of 4'-hydroxyclobazam and 4'-hydroxy-N-desmethyl-clobazam. The main urinary metabolites are N-desmethyl-clobazam and 4'-hydroxy-clobazam. In man, the plasma elimination phase of unchanged clobazam varies with age and sex. In one study, after a single dose of 20 mg, the following half-lives were observed :- young men 17 hours; young women 31 hours; elderly men 48 hours; elderly women 49 hours.

A steady level of clobazam in the plasma is reached within 1 week of initiating treatment or changing the dose. The plasma beta elimination phase of the major plasma metabolite, N-desmethyl-clobazam is considerably longer and is about 2 to 3 days for young men and women and 3 to 5 days for elderly men and women. It may increase with repeated doses. In a repeated dose study following administration of 10 mg clobazam twice daily for 28 days, the level of unchanged clobazam reached a steady state of 333 nanogram/mL within one week whereas the major serum metabolite took 28 days to reach a near steady state level about 8 times higher than that of unchanged clobazam and this was from 8.3 to 27.5 times higher than the metabolite level after a single dose. The levels fell slowly after the last dose from 2,811 nanogram/mL to 2,031 nanogram/mL on the 7th day.

Age and sex influence the metabolism of clobazam in that the total clearance of clobazam is significantly lower in the elderly male and elimination half life is extended in both the elderly male and female which leads to the accumulation of the parent compound and its active metabolite. Lower dosage should be given to these patients.

Excretion

Over a two week period approximately 79% of a 20 mg oral dose of clobazam is excreted in the urine and 12% in the faeces as parent drug and/or metabolites.

Indications

Adjunctive therapy in partial or generalised epilepsy and monotherapy in certain forms of epilepsy such as Lennox-Gastaut and catamenial epilepsy.

Contraindications

Hypersensitivity to clobazam or other benzodiazepines or excipients.

Myasthenia gravis.

Severe respiratory insufficiency or chronic obstructive airway disease with incipient respiratory failure.

History of drug or alcohol dependence.

Sleep apnoea syndrome.

Severe impairment of liver function.

Pregnancy (see 'Precautions' – Use in Pregnancy)

Lactation (see 'Precautions' – Use in Lactation)

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

Frisium has been shown to have a less detrimental effect on psychomotor performance than 1,4-benzodiazepines (diazepam, lorazepam) in experimental studies in volunteers at doses of 10 to 30mg/day. However, as with all patients taking CNS-depressant medications, patients receiving Frisium should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from Frisium therapy. Abilities may be impaired on the day following use.

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of Frisium.

Following the use of Frisium at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. The minimum time is probably four weeks, although programmes as long as four months have been suggested. As with all benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use (see Precautions, Dependence). A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (eg Frisium) to one with a short duration of action.

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of Frisium is not recommended. There is evidence that tolerance develops to the sedative effect of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (eg. rebound insomnia following cessation of a hypnotic benzodiazepine).

Precautions

Use in elderly or debilitated patients

Dosage should be limited to the smallest effective amount to reduce the possibility of a fall due to sedation, giddiness, confusion or ataxia.

Hypotension

Although hypotension occurs uncommonly, Frisium should be administered with care to patients in whom a drop in blood pressure may lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Epilepsy

When benzodiazepines are administered to persons with convulsive disorders, there is a possibility that the frequency and/or severity of seizures may increase and require an adjustment of anticonvulsant medication (development of tolerance). There is some evidence that concurrent administration of Frisium with phenobarbitone, phenytoin or carbamazepine may marginally increase the blood levels of the anticonvulsants and also increase the rate of metabolism of Frisium. Increases in valproic acid levels with Frisium treatment, have also been observed in a study involving six patients. Therefore the blood levels of the anticonvulsants should be determined

in such cases. Abrupt withdrawal of benzodiazepine should be avoided, as this may temporarily increase seizure frequency and severity.

Amnesia

Amnesia, usually anterograde but extending sometimes to the period preceding drug administration, has been frequently reported after parenteral administration and less frequently after oral doses of benzodiazepines.

Paradoxical reactions

Paradoxical reactions such as rage, stimulation or excitement may occur rarely with Frisium and are an indication to discontinue the drug.

Thyroid adenomas

A dose related increase in thyroid adenomas was observed in a 2 year study in rats.

Acute intoxication with CNS depressant drugs

Frisium may potentiate the effects of CNS depressant drugs; therefore the administration of Frisium should be cautious in cases of acute intoxication with alcohol, hypnotics, analgesics, neuroleptics, antidepressants and lithium (See Interactions with other Medicines).

In patients with pre-existing muscle weakness or spinal or cerebellar ataxia, special observation is required and a dose reduction may be necessary.

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired Renal/Liver Function and Blood Dyscrasias

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver and kidney function tests are recommended.

Depression, Psychosis and Schizophrenia

Frisium is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Impaired Respiratory Function

Caution in the use of Frisium is recommended in patients with respiratory depression and in patients with chronic or acute respiratory insufficiency. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. Respiratory function must be monitored and a dose reduction may be necessary.

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.

Abuse

Caution must be exercised in administering Frisium to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence

The use of benzodiazepines may lead to dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance as defined by a need to increase the dose in

order to achieve the same therapeutic effect seldom occurs in patients receiving recommended dose under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms range from headaches, sleep disturbances, increased dreaming, tension, restlessness, confusion, excitability, symptomatic psychoses (eg withdrawal delirium), numbness and tingling sensations in extremities, muscle pain, sweating, nausea and vomiting, hyperacusis, epileptic seizures, insomnia, anxiety, dysphonia, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations, (e.g. feelings of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly Frisium should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia, mood changes, anxiety or sleep disturbances and restlessness mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Use in Pregnancy

Category C

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function, respiratory depression, hypothermia and difficulties drinking (signs and symptoms of so-called "floppy infant syndrome") in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

Use in Lactation

Frisium may appear in the breast milk of nursing mothers and may cause drowsiness and feeding difficulties in the infant. For this reason, the use of Frisium in such circumstances cannot be recommended. Neonates are generally more susceptible to the toxic effects of benzodiazepines.

Use in the Elderly

Dosage should be limited to the smallest effective amount to reduce the possibility of a fall due to sedation, giddiness, confusion or ataxia. (see 'Precautions' - Tolerance and Dependence).

Carcinogenicity

In a carcinogenicity study, a significant increase in thyroid follicle cell adenoma was found in rats in the highest dose group (100 mg/kg body weight).

Clobazam – like other benzodiazepines – leads to activation of the thyroid in rats. These changes have not been observed in investigation in other species.

Genotoxicity

Clobazam had no known genotoxic or mutagenic effects

Interactions with other Medicines

The benzodiazepines, including Frisium, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, hypnotics, narcotic analgesics, anxiolytics, anticonvulsants and anaesthetics (see Precautions). Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or lithium.

Frisium undergoes oxidative metabolism, and consequently may interact with disulfiram or cimetidine resulting in increased plasma levels of benzodiazepines. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with drugs that inhibit the cytochrome P-450 enzyme (mono-oxygenase) system (eg. either disulfiram, erythromycin or cimetidine); some patients may require a reduction in benzodiazepine dosage.

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together. ECG monitoring should be performed and serum level monitoring of the anticonvulsant be performed more frequently.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

Patients should be advised of possible interactions, especially with alcohol, as bioavailability of clobazam can be increased by 50%.

If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

Carbamazepine and phenytoin may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethyl clobazam.

The effects of muscle relaxants and nitrous oxide may be enhanced.

Effect on Laboratory Tests

Data not available.

Adverse Effects

The following side effects have been reported: dizziness, drowsiness, dry mouth, headache, nausea, constipation, loss of appetite and fine tremor of fingers, prolonged reaction time, ataxia, numbed emotions, muscle weakness and confusion.

Another possibility is the emergence of paradoxical reactions (eg. restlessness, irritability, anxiety, suicidal tendencies acute agitational states, aggressiveness, delusions, fits of rage, nightmares, hallucinations, psychotic reactions, frequent muscle spasms and insomnia). In the event of such reactions, treatment with clobazam should be discontinued.

Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range but especially at higher dose levels. Amnestic effects may be associated with inappropriate behaviour. Pre existing depression may be unmasked during benzodiazepine use.

Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (eg bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate.

After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, has been reported in very rare cases, particularly in elderly patients. It sometimes persists for some length of time.

There may be reversible abnormalities, such as disorders of articulation (slow or indistinct speech), visual disturbances (eg. double vision, nystagmus), unsteadiness of gait and other motor functions, weight gain or loss of libido, especially in patients receiving high doses or long term treatment.

Cutaneous reactions, such as urticaria, pruritis, exanthema may develop in rare cases.

When used as an adjuvant in the treatment of epilepsy, this preparation may in rare cases cause restlessness and muscle weakness.

Tolerance and dependence may develop, especially with prolonged use.

Dosage and Administration

Adults:

20 - 30 mg daily in divided doses or as a single dose at night. Maximum dose 60 mg.

Children and Elderly Patients:

Half the adult dose.

Small doses should be used initially, 5-15mg/day, gradually increasing to a maximum daily dose of 60mg/day, as directed by the doctor. The possible interference with alertness and reaction time must be taken into account. The fundamental principle is to keep the dose as low as possible. Constant doses, eg. 20mg/day and intermittent therapy, discontinuing clobazam and subsequently prescribing it again, have proved effective. If the daily dose is divided, the higher proportion should be taken at night.

Daily doses up to 30mg may be taken as a single dose at night.

Children over 3 years and elderly patients receive half the daily dose recommended for adults. Clobazam should not normally be given to children between the age of 6 months and 3 years, unless it is strictly indicated.

In patients with impaired liver and kidney function, the dosage should be reduced. Increased responsiveness and higher susceptibility to adverse effects may be present in children and elderly patients and require low initial doses and gradual dose increments under careful observation

When clobazam is to be discontinued after prolonged administration, the dose should be tapered off over a period of time. Treatment with clobazam should not be continued for more than 4 weeks without medical supervision.

Overdosage

Overdosage 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, coma and very rarely death

Treatment : In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken. Activated charcoal should be given to reduce absorption if the patient is conscious. Hypotension and respiratory depression should be managed according to general principles. Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

Contact the Poisons Information Centre for advice on management of overdosage.

Presentation and Storage Conditions

Each Frisium tablet is white, scored on one side with the letter 'B' on one side of the score line and 'GL' on the other. The reverse side features the Hoechst corporate logo.

Each pack of Frisium contains 50 tablets as 5 x 10 blister strips.

Store below 30°C.

Medicine Classification

Controlled Drug C5.

Further Information

Nil.

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Date Of Preparation

Approved December 1998

Date of Last Amendment: 15 October 2007