

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

 **FRISIUM®**  
(clobazam)

Tablets, 10 mg

Prescribed

Antiepileptic

Manufactured by:  
Lundbeck  
Four Parkway North  
Deerfield, IL 60015, U.S.A.

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**FRISIUM®**  
(clobazam)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Tablet 10 mg	Lactose  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

FRISIUM (clobazam) is indicated for:  
adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

**Geriatrics (> 65 years of age):**

The efficacy of FRISIUM in adults aged 65 and over has not been established (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY sections).

**CONTRAINDICATIONS**

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. These reactions may not be limited to rash, urticaria, and hypotension. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- myasthenia gravis (risk of aggravation of muscle weakness)
- narrow angle glaucoma
- any history of drug or alcohol dependence (increased risk of development of dependence)
- severe respiratory insufficiency
- sleep apnoea syndrome (risk of deterioration)
- severe impairment of liver function (risk of precipitating encephalopathy)
- during first trimester of pregnancy and breast-feeding (see WARNINGS AND PRECAUTIONS section)

## **WARNINGS AND PRECAUTIONS**

### **General**

FRISIUM can cause muscle weakness. FRISIUM is contraindicated in patients with myasthenia gravis. In patients with pre-existing muscle weakness or with spinal or cerebellar ataxia, special observation is required and a dose reduction may be necessary (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION sections).

Additive effects are to be expected if FRISIUM is combined with alcohol or drugs with central nervous system depressant effects. Moreover, concomitant consumption of alcohol can increase the serum levels of FRISIUM by 50%.

Patients should therefore be advised against consumption of alcohol during treatment with FRISIUM due to an increased risk of sedation and other adverse effects (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).

FRISIUM possesses a mild central nervous system depressant effect. Under experimental conditions, impairment of alertness has been observed to be less pronounced after therapeutic doses of FRISIUM than after other benzodiazepines. Nevertheless, even when used as directed, FRISIUM may alter reactivity to such an extent as to impair driving performance or the ability to operate machinery, especially when it is taken in conjunction with alcohol. Therefore patients should be cautioned against driving, operating dangerous machinery or engaging in other hazardous activities, particularly in the dose adjustment period, or until it has been established that they do not become drowsy, dizzy or develop muscle weakness.

### **Dependence/Tolerance**

Physical and psychological dependence are known to occur in persons taking benzodiazepines. FRISIUM should not be administered to individuals prone to drug abuse. Caution should be observed in all patients who are considered to have potential for psychological dependence. The risk of dependence increases with the dose and duration of treatment. However, this risk is present even with daily intake of FRISIUM 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. As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use. These patients or those who may increase the dose on their own initiative must be closely monitored.

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

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

The rebound phenomenon is characterized by a recurrence in enhanced form of the symptoms which originally led to FRISIUM treatment (i.e. 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 FRISIUM treatment will lead to withdrawal symptoms. These may include headaches, insomnia, sleep disturbances, increased dreaming, restlessness, tension, mental impairment, confusion, extreme anxiety, excitability, irritability, nervousness, agitation, derealization, depersonalization, hallucinations and symptomatic psychoses (e.g. withdrawal delirium), numbness and tingling sensations in the extremities, muscle pain, tremors, sweating, diarrhea, abdominal cramps, vomiting, nausea, hyperacusis, hypersensitivity to light, noise and physical contact, convulsions, as well as epileptic seizures.

As with other benzodiazepines, FRISIUM should be withdrawn gradually (see WARNINGS AND PRECAUTIONS section).

Loss of part or all of the anticonvulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time. There is no absolute or universal definition for the phenomenon and reports vary widely on its development.

The reported success of clobazam in intermittent therapy in catamenial epilepsy implies that tolerance may be minimized by intermittent treatment but long-term follow-up is unreported. No studies have identified or predicted which patients are likely to develop tolerance or precisely when this might occur.

### **Hepatic/Biliary/Pancreatic**

FRISIUM is contraindicated in patients with severe liver dysfunction. In patients with a lesser degree of liver dysfunction (mild to moderate hepatic impairment), responsiveness to FRISIUM and susceptibility to adverse effects are increased. These patients require low initial doses and gradual dose increments under careful observation (see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY sections). In long-term treatment, hepatic function must be checked regularly.

### **Neurologic**

In clinical trials, somnolence or sedation was reported at all effective doses, especially at the beginning of treatment with FRISIUM and when higher doses are used.

Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. Patients should be advised that sedation can occur, particularly early in treatment or with dose increases. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of FRISIUM is known.

Anterograde amnesia is known to occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with

inappropriate behaviour.

## **Psychiatric**

**Suicidal Ideation and Behaviour:** Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

Patients with a history of depression and/or suicide attempts should be kept under close supervision. All patients treated with antiepileptic drugs (AEDs), irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which AEDs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known. There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (AED or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (AED or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more AEDs). Therefore, the small increased risk of suicidal ideation and behavior reported from the meta-analysis (0.43% for patients on AEDs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (AED or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and behaviour for patients with epilepsy that are taking AEDs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct AED treatment in both arms.

It should be recognized that suicidal tendencies may be present in patients with emotional disorders; particularly those depressed. Protective measures and appropriate treatment may be necessary and should be instituted without delay. Pre-existing depression may be unmasked during benzodiazepine use.

Since excitement and other paradoxical reactions can result from the use of benzodiazepines in psychotic patients, FRISIUM should not be used in patients suspected of having psychotic tendencies.

FRISIUM is not recommended for use in patients with depressive disorders or psychosis.

## **Renal**

The pharmacokinetics of clobazam were evaluated in patients with mild and moderate renal impairment. There were differences in systemic exposure (AUC and C<sub>max</sub>) observed between patients with mild or moderate renal impairment and healthy subjects; the clinical relevance of these changes is not known. These patients require low initial doses and gradual dose increments under careful observation (see DOSAGE AND ADMINISTRATION section). There is no experience with FRISIUM in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or its active metabolite, N-desmethyclobazam, is dialyzable. In long-term treatment, renal function must be checked regularly.

## **Respiratory**

FRISIUM can cause respiratory depression, especially if administered in high doses. In elderly patients these effects sometimes persist for a considerable length of time. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with FRISIUM. FRISIUM is contraindicated in patients with severe respiratory insufficiency or sleep apnoea syndrome. In patients with a lesser degree of acute or chronic, respiratory insufficiency, respiratory function should be monitored and a dose reduction may be necessary (see CONTRAINDICATIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

It is recognized that patients with epilepsy are at increased risk for aspiration due to recurrent seizures and that this risk is increased by the high co-morbidities seen in patients with LGS. Benzodiazepines, including FRISIUM, may increase the risk of pneumonia from a decreased ability to manage secretions. The risk of pneumonia increases with the dose level of FRISUM (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

## **Skin**

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with FRISIUM in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. FRISIUM should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered.

## ***Special Populations***

**Pregnant Women:** There are no adequate and well-controlled studies of clobazam in pregnant women.

The available animal data suggest developmental toxicity, including an increased incidence of fetal abnormalities following oral administration of clobazam to pregnant animals at doses

similar to those used clinically.

Data for other benzodiazepines suggest the possibility of adverse effects in animals and humans. Long-term effects on neurobehavioural and immunological function have been reported in rodents following prenatal exposure to benzodiazepines.

Clobazam crosses the placental barrier. Several studies have suggested an increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during the first trimester of pregnancy. FRISIUM must not be used in the first trimester of pregnancy. In the later stages of pregnancy, it must only be used if there are compelling indications. If FRISIUM is prescribed to a woman of child-bearing potential she should be warned to consult her physician regarding the discontinuation of the drug if she intends to become, or suspects she might be, pregnant.

Neonatal flaccidity, respiratory and feeding difficulties, hypothermia, and withdrawal symptoms have been reported in infants born to mothers who received benzodiazepines, including clobazam, late in pregnancy. Administration of high doses of FRISIUM immediately before or during childbirth can provoke the occurrence of hypothermia, hypotonia, respiratory depression, and difficulties in drinking in the newborn infant. 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.

**Nursing Women:** Nursing mothers in whom therapy with FRISIUM is indicated should cease breast-feeding, since FRISIUM passes into breast milk.

**Geriatrics (> 65 years of age):** FRISIUM should be used with caution in elderly and debilitated patients, and those with organic brain disorders, with treatment initiated at the lowest possible dose (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY sections).

Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the CNS depressant activity of benzodiazepines even after low doses. Manifestations of this CNS depressant activity include ataxia, oversedation and hypotension. Therefore, medication should be administered with caution to these patients, particularly if a drop in blood pressure might lead to cardiac complications. Initial doses should be low and increments should be made gradually, depending on the response of the patient, in order to avoid oversedation, neurological impairment and other possible adverse reactions. After prolonged use of benzodiazepines, impairment of consciousness, sometimes combined with respiratory disorders, has been reported in very rare cases, particularly in elderly patients; these effects sometimes persist for a considerable length of time (see ACTION AND CLINICAL PHARMACOLOGY section).

## **Monitoring and Laboratory Tests**



If FRISIUM is administered for repeated cycles of therapy, periodic blood counts and liver, renal and thyroid function tests are advisable.

## **ADVERSE REACTIONS**

From 19 published studies of FRISIUM use in epileptic patients, the overall incidence of side-effects was 33% of which drowsiness, dizziness and fatigue were most frequently reported. Canadian experience provides a similar overall incidence (32%) with drowsiness reported in 17.3% of patients, and 12% of patients terminating treatment because of side-effects.

The incidence of side-effects was lower in patients under 16 years of age (23.7%) than the incidence in adults (43.1%):  $p < 0.05$ , whereas treatment discontinuation incidences were similar across age groups: 10.6% and 13.8% respectively. The following side-effects occurred at incidences of greater than 1% (ataxia [3.9%], weight gain [2.2%], dizziness [1.8%], nervousness [1.6%], behaviour disorder [1.4%], hostility and blurred vision [1.3%]).

Other side effects below included:

**Blood and lymphatic system disorders:** Anemia, eosinophilia, leukopenia, thrombocytopenia

**Eye disorders:** Double vision, nystagmus

**Gastrointestinal disorders:** Dry mouth, constipation, loss of appetite, nausea, weight gain, increased appetite, vomiting, abdominal distention

**General disorders and administration site conditions:** Unsteadiness of gait and other motor functions, fatigue, sedation leading to tiredness and sleepiness, especially at the beginning of treatment and when higher doses are used, slowing of reaction time, drowsiness, slow or indistinct speech, irritability, hypothermia

**Immune system disorders:** Hypersensitivity (see CONTRAINDICATIONS section)

**Investigations:** Hepatic enzyme increased

**Infections and infestations:** Pneumonia

**Musculoskeletal and connective tissue disorders:** Muscle weakness, frequent muscle spasms

**Nervous system disorders:** Altered state of consciousness, anterograde amnesia, somnolence, lethargy hyporesponsive to stimuli, disorientation, confusion, headaches, tremor, fine tremor of the fingers, dysarthria, psychomotor hyperactivity

**Renal and urinary disorders:** Urinary retention

**Psychiatric disorders:** Suicidal behaviour and ideation, psychotic reactions, hallucination,

delusion, acute agitational states, anxiety, emotional disorder, flat affect, aggressiveness, anger, fits of rage, restlessness, difficulty falling asleep or sleeping through, insomnia, nightmare, loss of libido

**Respiratory, thoracic and mediastinal disorders:** Respiratory distress, respiratory depression, aspiration pneumonia, cough

**Skin and subcutaneous tissue disorders:** Rash, urticaria, exanthema, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) (see WARNINGS AND PRECAUTIONS section)

### **Additional Explanatory Information for Post-Market Adverse Drug Reactions**

FRISIUM may cause sedation leading to tiredness and sleepiness, especially at the beginning of treatment and when higher doses are used.

Slowed or indistinct speech, unsteadiness of gait and other motor functions, visual disorders (nystagmus, double vision), weight gain, or loss of libido may occur. Such reactions occur particularly with high doses or following prolonged use, but are reversible.

Paradoxical reactions may occur, especially in children and in the elderly. These may include restlessness, difficulty falling asleep or sleeping through, irritability, acute agitational states, anxiety, aggressiveness, delusion, fits of rage, nightmares, hallucinations, psychotic reactions, suicidal tendencies, or frequent muscle spasms. In the event of such reactions, treatment with FRISIUM must be discontinued.

Tolerance and dependence may develop, especially during prolonged use.

Anterograde amnesia may occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour.

FRISIUM may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with the use of FRISIUM. In a 15 week Lennox-Gastaut Syndrome placebo-controlled trial, the frequency of pneumonia increased from 2% in the placebo group, up to 7 % in clobazam-exposed patients with a maximum daily dose of 20 mg for  $\leq 30$  kg/body weight and 40 mg for  $> 30$  kg/body weight.

### **Post-market clinical trial adverse events in Lennox-Gastaut Syndrome patients**

For the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS), clobazam was administered to 333 healthy volunteers and 300 patients with a current or prior diagnosis of LGS, including 197 patients treated for 12 months or more. The conditions and

duration of exposure varied greatly and included single- and multiple-dose clinical pharmacology studies in healthy volunteers and two double-blind studies in patients with LGS (Study 1 and 2). Only Study 1 included a placebo group, allowing comparison of adverse reaction rates on clobazam at several doses to placebo.

Study 1 (N=238) was a randomized, double-blind, placebo-controlled study consisting of a 4-week baseline period followed by a 3-week titration period and 12-week maintenance period. Study 2 (N=68) was a randomized, double-blind comparison study of high- and low-dose clobazam, consisting of a 4-week baseline period followed by a 3-week titration period and 4-week maintenance period.

**Table 1 – Treatment-emergent Adverse Events (TEAEs) Reported for ≥ 5% of Patients and More Frequently than Placebo in any Treatment Group**

	Placebo N=59 %	Clobazam Dose Level			All Clobazam N=179 %
		Low <sup>a</sup> N=58 %	Medium <sup>b</sup> N=62 %	High <sup>c</sup> N=59 %	
<b>Gastrointestinal Disorders</b>					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
<b>General Disorders and Administration Site Conditions</b>					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
<b>Infections and Infestations</b>					
Upper respiratory tract infection	10	10	13	14	12
Pneumonia	2	3	3	7	4
Urinary tract infection	0	2	5	5	4
Bronchitis	0	2	0	5	2
<b>Metabolism and Nutrition Disorders</b>					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
<b>Nervous System Disorders</b>					
Somnolence or Sedation	15	17	27	32	26
Somnolence	12	16	24	25	22
Sedation	3	2	3	9	5
Lethargy	5	10	5	15	10
Drooling	3	0	13	14	9

Ataxia	3	3	2	10	5
Psychomotor hyperactivity	3	3	3	5	4
Tremor	0	2	7	2	3
Dysarthria	0	2	2	5	3
<b>Psychiatric Disorders</b>					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
<b>Respiratory Disorders</b>					
Cough	0	3	5	7	5
Nasal congestion	2	5	0	2	2
<b>Skin and subcutaneous tissue disorders</b>					
Rash	3	2	3	5	3

<sup>a</sup>0.25 mg/kg/day; tablets; orally; for 15-18 weeks

<sup>b</sup>0.5 mg/kg/day; tablets; orally; for 15-18 weeks

<sup>c</sup>1.0 mg/kg/day; tablets; orally; for 15-18 weeks

The adverse reactions associated with clobazam treatment discontinuation in  $\geq 1\%$  of patients in decreasing order of frequency included lethargy, somnolence, ataxia, aggression, fatigue, and insomnia.

## DRUG INTERACTIONS

### Overview

Clobazam is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with clobazam. Additional non-hormonal forms of contraception are recommended when using FRISIUM.

Clobazam inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary.

Concomitant administration of drugs that inhibit the cytochrome P-450 enzyme system may enhance and prolong the action of FRISIUM.

In summary, if FRISIUM is administered simultaneously with other antiepileptic drugs, the dosage must be adjusted under regular medical supervision (EEG monitoring), as there may be interactions with the patient's basic anticonvulsant medication. Blood levels monitoring of concomitant medication is advisable.

### Drug-Drug Interactions

Most studies of the potential interactions of clobazam with other antiepileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine, with the exception of one. This one study noted that the addition of clobazam caused a 25% increase in serum drug levels in 29% of patients taking carbamazepine, 63% of patients taking phenytoin, 13% of those taking valproate and 14% of those on phenobarbital. The contradictory findings in different studies are presumably due to variations in patient susceptibility, and although clinically significant interactions are unusual, they may occur.

**Table 2 - Established or Potential Drug-Drug Interactions**

<b>Clobazam</b>	<b>Ref</b>	<b>Effect</b>	<b>Clinical comment</b>
Carbamazepine, phenytoin, phenobarbital, valproate	CT	Caused the blood levels of clobazam to decrease slightly  With regard to N-desmethyloclobazam: serum levels are lower with valproate but higher with carbamazepine and phenytoin.	Monitor blood levels of antiepileptic agents, and adjust dose accordingly under medical supervision should it be clinically warranted
Diphenylhydantoin	CT	Caused the blood levels of clobazam to decrease slightly  With regard to N-desmethyloclobazam: serum levels are higher with diphenylhydantoin.	Monitor blood levels of antiepileptic agents, and adjust dose accordingly under medical supervision should it be clinically warranted
Strong CYP2C19 inhibitors e.g., fluconazole, fluvoxamine, ticlopidine  Moderate CYP2C19 inhibitors e.g., omeprazole	CT	May result in increased exposure to N-desmethyloclobazam, the active metabolite of clobazam. This may increase the risk of dose-related adverse reactions.	Dosage adjustment of clobazam may be necessary when coadministered

Alcohol	CT	May significantly increase plasma clobazam levels by approximately 50%	Patients should be cautioned about the possibility of additive effects when FRISIUM is combined with alcohol (see WARNINGS AND PRECAUTIONS section)
Other central nervous system depressant drugs e.g. antipsychotics, anxiolytics, certain antidepressant agents, anticonvulsant drugs, sedative antihistamines, anaesthetics, hypnotics or narcotic analgesics, or other sedatives	CT	Especially when clobazam is administered in higher doses, a mutually potentiating effect is to be expected if administered or alcohol is consumed at the same time. Concomitant use of clobazam with other CNS depressants may increase the risk of sedation and somnolence	Special precaution is necessary when clobazam is administered in cases of intoxication with such substances (see WARNINGS AND PRECAUTIONS section)
Lithium	CT	Mutually potentiating effect is to be expected	Special precaution is necessary when clobazam is administered in cases of intoxication with lithium (see WARNINGS AND PRECAUTIONS section)
Narcotic analgesics	CT	Possible euphoria may be enhanced; this may lead to increased psychological dependence	Special precaution is necessary
Muscle relaxants and nitrous oxide	CT	The effects may be enhanced	Special precaution is necessary

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

### Drug-Food Interactions

The administration of food with clobazam has variable effects on the rate of absorption.

### Drug-Herb Interactions

Interactions with herbs have not been studied.

### Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- Dosage and duration of treatment must be adjusted to 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.
- **Patients with impaired liver or renal function:** FRISIUM should be used at a reduced dosage in these patients, including CYP2C19 poor metabolizers (see WARNINGS AND PRECAUTIONS section).
- **Use in patients with acute, or chronic respiratory insufficiency:** In patients with a lesser degree of acute or chronic, respiratory insufficiency, respiratory function should be monitored and a dose reduction of FRISIUM may be necessary (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).
- **Use in patients with pre-existing muscle weakness or with spinal or cerebellar ataxia:** In patients with pre-existing muscle weakness or with spinal or cerebellar ataxia, special observation is required and a dose reduction of FRISIUM may be necessary (see WARNINGS AND PRECAUTIONS section).
- 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.

### Recommended Dose and Dosage Adjustment

Tablets for oral use.

**Adults:** Small doses, 5-15 mg/day, should be used initially, gradually increasing to a maximum daily dose of 80 mg as necessary.

**Children from 2 to 16 years:** The initial dose in children should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day.

**Infants  $\leq$  2 years:** In infants, the initial daily dose is 0.5-1 mg/kg/day.

**Elderly:** Due to decreased organ function in elderly patients, lower initial doses and gradual dose increments are recommended and patients should be monitored for responsiveness and adverse events.

**CYP2C19 Poor metabolizers:** In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be the lowest initial recommended dose and dose titration should proceed slowly, as tolerated according to the age group, but to half the maximum dose described. If necessary and based upon clinical response, an additional titration to the maximum dose (depending on the age group) may be started on day 21.

**Hepatic Impairment:** Patients with mild to moderate hepatic impairment require low initial doses and gradual dose increments under careful observation. Therefore, the starting dose in these patients should be the lowest initial recommended dose and dose titration should proceed slowly, as tolerated according to the age group, but to half the maximum dose described. If necessary, and based upon clinical response, an additional titration to the maximum dose (depending on the age group) may be started on day 21. There is inadequate information about metabolism of clobazam in patients with severe hepatic impairment (see CONTRAINDICATIONS section).

As with all benzodiazepines, abrupt withdrawal may precipitate seizures as well as other withdrawal symptoms. It is therefore recommended that FRISIUM be gradually reduced in dose before treatment is discontinued. Taper by decreasing the total daily dose by 5-10 mg/day, on a weekly basis until discontinued.

As with other benzodiazepines, the possibility of a decrease in anticonvulsant efficacy in the course of treatment must be borne in mind.

If the daily dose is divided, the higher portion should be taken at night. Daily doses up to 30 mg may be taken as a single dose at night.

#### **Missed Dose**

If a patient misses a dose of FRISIUM, they should take it as soon as they remember. If they are close to their next dose, they should just take their next dose, without making up for the missed dose. They should not take 2 doses at the same time.

#### **Administration**

The tablets are administered whole or broken in half along the score.

#### **OVERDOSAGE**

**Symptoms:** Overdose and intoxication with benzodiazepines - including FRISIUM - may lead to central nervous depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, reduced reflexes, increasing sedation, respiratory depression, hypotension and, rarely, coma or death. The risk of fatal outcome is increased in cases of combined poisoning with other central nervous system depressants, including alcohol.

Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and overstimulation usually when the effects of the drug begin to wear off.

**Treatment:** It is recommended that the possible involvement of multiple agents be taken into consideration. Consciousness, respiration, pulse rate and blood pressure should be monitored. If respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of



intravenous fluids started. Immediate gastric lavage may be beneficial if performed soon after ingestion of FRISIUM. Secondary elimination of clobazam, by forced diuresis or hemodialysis, is ineffective. Facilities for the management of complications such as airway obstruction or respiratory insufficiency must be available. Hypotension can be treated by replenishment with plasma substitutes and, if necessary, with sympathomimetic agents.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Clobazam is a 1,5-benzodiazepine with anticonvulsant properties.

The exact mechanism of action for clobazam, a 1,5-benzodiazepine, is not fully understood but is thought to involve potentiation of GABAergic neurotransmission resulting from greater binding at the benzodiazepine site of the GABA<sub>Aα2</sub> receptor.

In general, the mode of antiepileptic action of clobazam is probably largely analogous to that of the 1,4-benzodiazepines. The differences between clobazam (a 1,5-benzodiazepine) and the 1,4-benzodiazepines in terms of therapeutic efficacy and neurotoxicity are possibly due to the variation in degree of the agonist action at the high affinity benzodiazepine receptor or to differing relative action at the high and low affinity benzodiazepine receptors.

### **Pharmacodynamics**

Electrophysiological studies have shown that benzodiazepines potentiate GABA-ergic transmission at all levels of the neuroaxis, including the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex. The changes induced by the interaction of GABA with its receptors are enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain.

### **Electrocardiography**

The effect of clobazam on ECG interval parameters was evaluated in a randomized, double-blind, double-dummy, placebo-, and active-controlled parallel thorough QT study in 280 healthy subjects (70/treatment group). Study medication was administered on Days 1 through 29. Clobazam was titrated to doses of 40 mg/day (20 mg twice daily) and 160 mg/day (80 mg twice daily), with only the morning dose administered on Day 29. ECG assessments were performed at baseline and on day 29.

Clobazam was associated with QTcF shortening. The 90% confidence intervals for comparisons with placebo excluded zero at 10 of 13 time points in the clobazam 40 mg group, with a maximum mean difference from placebo of -5.3 ms (90% CI -7.5, -3.1) at 4 h post-dosing. For the clobazam 160 mg treatment group, the 90% confidence intervals excluded zero at all time points, with a maximum mean difference from placebo of -6.5 ms (90% CI -8.7, -4.3) at 4 h post-dosing. Clobazam had no noteworthy effect on the QRS duration.

Clobazam prolonged the PR interval. In the 40 mg group, small, but statistically significant, prolongation of the PR interval was observed at 8 of 13 post-dose time points, with a maximum mean difference from placebo of 4.5 ms (90% CI 2.6, 6.5) at 2 h. In the 160 mg group, statistically significant prolongation of the PR interval was observed at 8 of 13 post-dose time points, with a maximum mean difference from placebo of 3.9 ms (90% CI 1.9, 6.0) at 4 h.

Clobazam tended to increase heart rate. In the clobazam 40 mg group, small, but statistically significant, positive mean differences from placebo were observed at 7 of 13 time points, with a maximum mean difference of 3.4 bpm (90% CI 2.0, 4.9) at 6 h. In the clobazam 160 mg group, small, but statistically significant, positive mean differences from placebo were observed at 8 of 13 time points, with a maximum mean difference of 5.8 bpm (90% CI 4.3, 7.3) at 16 h.

### Pharmacokinetics

There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethyloclobazam to clobazam efficacy. Most reports indicate there is no, or only a very weak, correlation between the clobazam dose, or blood levels, and its clinical effects. Therapeutic blood levels for clobazam are in the range of 50 ng - 300 ng/mL with the corresponding range for N-desmethyloclobazam being from 1000- 4000 ng/mL. The serum levels at which anticonvulsant effects can be expected are not known but it can be assumed that the therapeutic range lies in the order of the figures given above. Since N-desmethyloclobazam blood levels are 10-20 times higher than those for clobazam, and this metabolite also has antiepileptic effects, it may be more important to the antiepileptic efficacy of clobazam than the parent compound itself.

**Absorption:** The oral absorption of clobazam, like that of all benzodiazepines, is fast and complete and amounts to at least 87%. Relative bioavailability of clobazam tablets or solution (in propylene glycol) is not significantly different. After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/ml) was observed after 0.25 to 4 hours. The administration of food with the drug has variable effects on the rate of absorption.

**Distribution:** Clobazam is highly lipophilic and distributes rapidly throughout the body, including fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The apparent volume of distribution at steady state was approximately 100 L. The *in vitro* plasma protein binding of clobazam and N-desmethyloclobazam is approximately 80-90% and 70%, respectively.

**Metabolism:** Clobazam is extensively metabolized in the liver. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. Main metabolites found in plasma are N-desmethyloclobazam and 4-hydroxyclobazam. N-desmethyloclobazam, an active metabolite, is the major circulating metabolite in humans. N-desmethyloclobazam is extensively metabolized, mainly by CYP2C19.

Lesser quantities of 4-hydroxy-N-desmethyloclobazam are also found. After a single dose of 30 mg clobazam, N-desmethyloclobazam attains maximum plasma concentrations after 24 to 72 hours.

**Excretion:** After oral administration of <sup>14</sup>C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. The half-life of N-desmethyloclobazam is much longer (mean 42 hours; range 36-46 hours) than for that of clobazam (mean 18 hours; range 10-30 hours).

### ***Special Populations and Conditions***

**Geriatrics:** The half-life of clobazam increases with the patient's age. In the elderly, there is a tendency to a reduction in clearance following oral administration; terminal half-life is prolonged and the distribution volume increased. This may lead to a more extensive accumulation of the drug when administered on a multiple-dose basis than in younger subjects. The effect of age on the clearance and accumulation profile of clobazam seems also to apply to the active metabolite (see WARNINGS AND PRECAUTIONS section).

**Gender:** Population pharmacokinetic analyses showed no difference in the clearance of clobazam between women and men.

**Race:** Population pharmacokinetic analyses including Caucasian (75%), African American (15%), and Asian (9%) subjects showed that there is no evidence of clinically significant effect of race on the clearance of clobazam.

**Hepatic Insufficiency:** There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. Hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. In patients with severe liver disease, the distribution volume of clobazam is increased and the terminal half-life is prolonged. Adjust dosage in patients with hepatic impairment (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS sections).

**Renal Insufficiency:** There were differences in plasma concentrations in patients with mild or moderate renal impairment compared to healthy subjects; the clinical relevance of these changes is not known. Patients with severe renal impairment or end stage renal disease (ESRD) were not studied (see WARNINGS AND PRECAUTIONS section).

### **STORAGE AND STABILITY**

FRISIUM tablets should be stored in their original containers.

Store at room temperature (15°C to 30°C).  
Keep in a safe place out of the reach and sight of children.

#### **SPECIAL HANDLING INSTRUCTIONS**

None

#### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

For oral use.

##### **Available under brand name of FRISIUM:**

FRISIUM 10 mg tablets are packaged in blisters of PVC film and aluminum foil and are distributed in packs of 30 tablets.

FRISIUM is available as white, uncoated, biconvex, round tablets of 7 mm in diameter, scored on one side. Each tablet is debossed with “**B**” above score line and “**GL**” below score line. Other side is debossed with the Hoechst “Tower and Bridge” logo.

FRISIUM tablets, 10 mg contain clobazam as active ingredient; colloidal silicon dioxide, lactose, magnesium stearate, starch (corn) and talc as non-medicinal ingredients.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

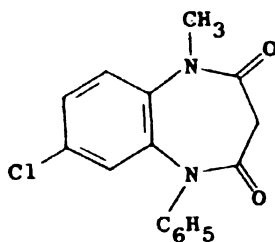
#### Drug Substance

Proper name: Clobazam [INN]

Chemical name: 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine-2,4(3H,5H)dione

Molecular formula and molecular mass:  $C_{16}H_{13}O_2N_2Cl$  and 300.7 respectively

Structural formula:



Physicochemical properties: White, odorless, crystalline powder. Soluble in chloroform and methanol. Very slightly soluble in water. Melting range of  $182 \pm 3^\circ\text{C}$ .

### CLINICAL TRIALS

Seven double-blind studies have been reported in which FRISIUM (clobazam) was given as adjunctive therapy versus placebo within an established antiepileptic regimen; FRISIUM was shown to be significantly superior to placebo.

### DETAILED PHARMACOLOGY

#### Drug interaction studies

##### *In vitro studies*

Clobazam did not inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A4, UGT1A6, or UGT2B4 *in vitro*. N-desmethyloclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4.

Clobazam and N-desmethyloclobazam did not significantly increase CYP1A2 or CYP2C19 activities, but did induce CYP3A4 activity. Clobazam and N-desmethyloclobazam also increased UGT1A1 mRNA but at concentrations much higher than observed plasma levels. The potential for clobazam or N-desmethyloclobazam to induce CYP2B6 and CYP2C8 has not been evaluated.

Clobazam and N-desmethyloclobazam do not inhibit P-glycoprotein (P-gp), but are P-gp substrates.

Strong (e.g., fluconazole, fluvoxamine, ticlopidine) and moderate (e.g., omeprazole) inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethyloclobazam, the active metabolite of clobazam, based on extrapolation from pharmacogenomic data. Dosage adjustment of clobazam may be necessary when coadministered with strong or moderate CYP2C19 inhibitors.

Alcohol has been reported to increase the maximum plasma exposure of clobazam by approximately 50%. Alcohol may have additive CNS depressant effects when taken with clobazam.

### Pharmacogenomics

The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active N-desmethyloclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethyloclobazam AUC and  $C_{max}$  are approximately 3-5 times higher in poor metabolizers (e.g., subjects with  $*2/*2$  genotype) and 2 times higher in intermediate metabolizers (e.g., subjects with  $*1/*2$  genotype). The prevalence of CYP2C19 poor metabolism differs, depending on racial/ethnic background. Dosage in patients who are known CYP2C19 poor metabolizers may need to be adjusted (see DOSAGE AND ADMINISTRATION section).

The systemic exposure of clobazam is similar for both CYP2C19 poor and extensive metabolizers.

### Pharmacodynamics - Animal Data

Pharmacologic studies in animals have shown that clobazam can suppress seizures induced by a variety of experimental procedures. With respect to electro-shock induced seizures in the mouse, clobazam is more effective than valproic acid but less effective than clonazepam.

Although comparison with diazepam and phenobarbital produced inconsistent results in this model, the anticonvulsant effects of all three substances can probably be regarded as similar.

The anticonvulsant effect of clobazam in acoustically induced seizures in the mouse was less marked than those of clonazepam and diazepam as shown by  $ED_{50}$ . In most cases however, in particular with chemically induced seizures, clobazam was more potent than the other antiepileptic agents: phenytoin, phenobarbital, carbamazepine and valproic acid (Table 5).

**Table 5 - Anticonvulsant activity of antiepileptic drugs in mice (chemically induced seizures) ( $ED_{50}$  [mg/kg orally])**

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	<b>Pentetrazol 125 mg/kg</b>	<b>Picrotoxin 15 mg/kg</b>	<b>Bicuculline 5 mg/kg</b>	<b>Isoniazid 600 mg/kg</b>	<b>Nicotine 1.5 mg/kg</b>	<b>Strychnine 1.2 mg/kg</b>
Clobazam	1.7	4.7	16.2	10.7	2.3	10.4
Diazepam	0.41	4.1	10	2.8	0.8	4.9
Clonazepam	0.038	2.3	1	0.075	0.14	>5
Phenobarbital	6.7	12.2	20.5	18.7	7.6	46.9
Phenytoin	7.6	3.6	10.4	21.8	19.8	>100
Carbamazepine	11.2	7.3	16.2	25	18.1	>100
Valproate	158	75.4	362	494	168	>800

Although the ED<sub>50</sub> is an important index, it is not a measure of the therapeutic value, since it has the disadvantage of not reflecting any undesired effects of the drug which might limit its subsequent use. The protective index (PI) is a more reliable indicator in this regard. The PI is equal to the quotient TD<sub>50</sub>/ED<sub>50</sub> where the TD<sub>50</sub> is the dose at which 50% of the animals in the Rota rod test show signs of ataxia. Hence, if the PI>1, anticonvulsant effects occur before the undesired ataxic effects. The greater the PI, the wider is the margin between the desirable anticonvulsant effect and the undesired ataxic effect. Comparing this index, clobazam was superior to diazepam, clonazepam, phenobarbital and valproic acid. Carbamazepine and phenytoin were sometimes inferior and sometimes superior to clobazam in the respective tests (Table 6).

**Table 6 - Protective indices of clobazam and other antiepileptics in tests on anticonvulsant activity in mice**

	<b>Electro-convulsive Seizures</b>	<b>Pentetrazol (tonic)</b>	<b>Pentetrazol (clonic)</b>	<b>Picrotoxin</b>	<b>Bicuculline</b>	<b>Isoniazid</b>	<b>Nicotine</b>	<b>Strychnine</b>
Clobazam	4.9	23.1	17.1	8.4	2.4	3.7	17.1	38
Diazepam	0.9	12.2	10	1.2	0.5	1.8	6.3	1
Clonazepam	0.6	9	7.1	0.2	0.3	4.5	2.4	<0.1
Phenobarbital	3.4	7	3	3.9	2.3	2.5	6.2	1
Phenytoin	14.6	13.3	<1	28.1	9.7	4.6	5.1	<1.0

Carbamazepine	12.6	9.1	<1	14	6.3	4.1	5.6	<1.0
Valproate	1.8	3	1.8	6.3	1.3	1	2.8	<1.0

Finally, the anxiolytic, sedative and myorelaxant effects of clobazam (a 1,5-benzodiazepine) were compared with those of 10 different 1,4-benzodiazepines. The ratios of specific effect to anticonvulsant effects showed that clobazam is a highly specific anticonvulsant.

### Pharmacokinetics - Animal Data

#### Absorption

After oral administration, absorption of clobazam was practically complete in all three animal species. Data are given in Table 7 which shows also maximum blood levels for the total concentration in the animal species examined and the times at which they were reached. Total concentration refers to clobazam and its metabolites.

**Table 7 - Blood levels after oral administration of <sup>14</sup>C-labelled clobazam**

Species	n	Maximum Total Concentration (µg/ml)	Time (H after application)	Dose (mg/kg)
Rat	6	0.046 ± 0.012	0.5	0.52
Dog	5	0.24 ± 0.043	22-4	0.5
Monkey	2	0.67 ± 0.82	0.5;1	2.5

#### Distribution

For serum concentrations between 0.05 and 10 µg/mL, the binding to serum proteins is shown in Table 8.

**Table 8 - Binding of <sup>14</sup>C-labelled clobazam to serum proteins**

Species	% Binding	Range Measured
rat	66 ± 2	0.05-10 µg/ml
dog	83 ± 2	0.05-10 µg/ml
monkey	76 ± 3	0.05-10 µg/ml



human	85 ± 3	0.05-10 µg/ml
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### Metabolism

Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied.

The two most important chemical changes of clobazam during metabolism are dealkylation and hydroxylation. Dealkylation at nitrogen-1, particularly pronounced in the dog, does not differ between the 1,4- and 1,5-benzodiazepines. However, hydroxylation at the 3-position which occurs with 1,4-benzodiazepines such as diazepam, does not occur with clobazam and may be a characteristic of 1,5-benzodiazepines in general.

### Elimination

Both after a single oral and intravenous dose, more than two-thirds of the drug-associated radioactivity is found in the faeces; dogs, however, excreted about 3/4 of the radioactivity with the urine, irrespective of the route of administration. In monkeys, the excretion also occurred mainly in the urine; in all three species, renal excretion was just as rapid as that from blood or plasma (Table 9). Elimination was almost completed after 48 hours in all species.

**Table 9 - Excretion after administration of <sup>14</sup>C-labelled clobazam to different animal species**

Species	Route of Administration	Dose mg/kg	Excretion (% administered dose)		
			Urine	Faeces	Balance
Rat	Intravenously	0.1	27 ± 1	73 ± 6	100 ± 6
Rat	Orally	0.52	29 ± 6	71 ± 7	100 ± 1
Dog	Intravenously	0.1	78 ± 9	28 ± 4	106 ± 2
Dog	Orally	0.5	74 ± 5	28 ± 2	192 ± 3
Monkey	Orally	2.5	61 ± 14	N.D.	

In several studies clobazam exhibited activity against seizures with doses usually ranging below those that cause disorders in motor activity (see Table 6). This separation is evident also with N-desmethyloclobazam. The advantage of clobazam compared with 1,4-benzodiazepines lies mainly in the fact that motor activity is influenced only after very high doses, these doses being

markedly above those required to induce tranquilizing and anti-aggression activities. In animal studies, clobazam had no marked effect on the cardiovascular system, respiration or excretion.

## **TOXICOLOGY**

### **Acute Toxicity**

In mice, the oral LD<sub>50</sub> was 640-1101 mg/kg, the intraperitoneal toxicity, 289-615 mg/kg, and the subcutaneous toxicity, 2250-2500 mg/kg. In rats, the oral LD<sub>50</sub> was 6000 mg/kg, the intraperitoneal LD<sub>50</sub>, 740-1526 mg/kg, and the subcutaneous toxicity, >5000 mg/kg. In rabbits, the oral LD<sub>50</sub> was 320 mg/kg whereas in guinea pigs it was 109 mg/kg. Signs exhibited during acute toxicity testing included somnolence, prostration, reduction in spontaneous motility, irregular breathing, ataxia, tremors, convulsions, loss of righting reflexes and reduction in body temperature. These were the most frequently observed signs in lethally poisoned animals.

### **Chronic Toxicity**

Clobazam was administered to rats in the diet or by gavage at doses of 0, 4, 12, 20, 25, 35, 100, 200, 400, 600 and up to 1000 mg/kg of body weight /day for periods ranging from 6 to 18 months. At 100 mg/kg for 6 months a transient slight growth retardation in males and in females a transient mild anemia and leucocytosis were observed. In the dose range of 12 to 1000 mg/kg of body weight/day, there was a dose-dependent reduction in spontaneous activity and, in the highest dose group, reduction in weight increase, respiratory depression and hypothermia were noted. Piloerection, lateral position, fall in body temperature, depression and death were observed in 4 treated with 100 mg/kg, in 3 treated with 400 mg/kg and in one control animal during the treatment period. Animals treated with 100 mg/kg for 2 weeks and subsequently changed to 200 mg/kg for up to the 36th week and then 600 mg/kg for the duration of the 18-month study showed dose-dependent increases in liver and thyroid and microscopic lesions, consisting of eosinophilic inclusions in the proximal convoluted tubules of the females and yellow granules in the livers of both males and females. The eosinophilic inclusions were accompanied by proliferation of the smooth endoplasmic reticulum.

Clobazam was administered to Beagle dogs at doses of 0, 2.5, 5, 10, 20, 40 and 80 mg/kg for periods ranging from 6 to 12 months. Dose-dependent symptoms were noted and consisted of sedation, ataxia, mild tremor, somnolence, emesis, seizures and progressive rise in serum alkaline phosphatase. At the 80 mg/kg dose for 6 months a significant increase in the weight of the liver was observed in males and females. In the 12-month study using 0, 5, 10 and 40 mg/kg a dose-dependent increased accumulation of pigments in hepatocytes and Kupffer cells was observed in the 5 mg/kg group. In another 12-month study where 0, 2.5 and 5 mg/kg doses were used there were yellow granules in the epithelial cells of the proximal convoluted tubules in the 5 mg/kg group at one year. The studies have shown that convulsions were observed on the second and third day after abrupt discontinuation of the drug.

In the one year study where 0, 5, 10 and 40 mg/kg of clobazam were used and in the 6-month study where 0, 5, 20 and 80 mg/kg were used, deaths occurred (9 and 2, respectively), but the

exact cause could not be ascertained. However, the animals experienced convulsive seizures with foaming at the mouth during the treatment period.

In a special study clobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 and up to 40 mg/kg daily for 16 months. Withdrawal symptoms were assessed beyond the fourth month of treatment following the interruption of medication on several occasions for 1 to 9 days. The incidence and the severity of the withdrawal symptoms were related to the duration of treatment and the greater susceptibility of the female than the male dog.

The withdrawal symptoms consisted of tremors, accelerated respiration, violent tonic-clonic convulsions, abundant salivation, frothing at the mouth, ptosis, sedation, ataxia stereotyped movements, gasping for breath, biting of the tongue. The symptoms usually subsided following reinstitution of medication.

N-desmethyloclobazam was administered orally to groups of 2 Beagle dogs (one male and one female) at doses of 0 up to 40 mg/kg daily for 12 months.

After 48 hours of drug withdrawal, symptoms occurred and consisted of short tonic-clonic convulsions and of relatively persistent tremor in the male dog whereas the female dog exhibited only a relatively persistent tremor.

Clobazam was administered to Rhesus monkeys by gavage at doses of 0, 2.5, 7.1 and 20 mg/kg for 52 weeks. Similar dose-dependent symptoms that were noted in dogs were also noted in monkeys. These consisted of sedation, somnolence, ataxia and mild tremor. There was a slight reduction in heart rate at 2.5 and 7.1 mg/kg. In addition, at 7.1 mg/kg sedation was observed. One male died in coma.

Signs of withdrawal appeared on the second day and these were aggression, piloerection, restlessness, little appetite and an unusual supine position. These withdrawal signs disappeared after readministration of clobazam.

In mouse, clobazam was associated with hepatomas in high-dose males. In rat, an increased incidence of thyroid adenomas was seen in males. There were three malignancies: two (male and female) in the thyroid and one (female) in the liver (see TOXICOLOGY, Carcinogenicity section). The relevance of these findings to man has not been established.

## **Reproduction and Teratology**

Clobazam was administered orally in the diet to rats and mice at doses up to 200 mg/kg/day for 60 days, during pairing, throughout pregnancy and for 21 days of post-natal development of the offspring. No effects on fertility in male and female animals and no effects on pregnancy or

course of labour were observed in mice with 200 mg/kg/day and in rats with 85 mg/kg/day. In rats, the offspring developed normally and their behaviour during the lactation period was unremarkable. In mice, litter sizes were normal, but a dose-dependent death rate of fetuses was observed in the highest dose group (200 mg/kg). In these litters, the dams did not bite through the umbilical cords and did not clean or nurse the offspring. This abnormality in the dams could have been compound induced after parturition. Liver weights were increased at the highest dose (200 mg/kg).

## **Carcinogenicity**

Carcinogenic studies were conducted in mice and in rats.

Clobazam was administered daily in the diet at doses of 0, 4, 20, and 100 mg/kg to groups of 60 male and 60 female CD-1 mice for 80 weeks.

Because of fighting in the group of males, male animals of the 100 mg/kg/day group were supplemented with a subgroup of 43 spare animals. Nine weeks after initiation of study, it was necessary to add a second subgroup of 42 spare animals.

The males of the supplemented subgroup treated with 100 mg/kg/day had more (8.3%) neoplastic changes (hepatomas) than the controls (1.7%) and the other treated male mice.

Clobazam was administered daily in the diet at doses of 0, 4, 20 and 100 mg/kg/day to groups of 60 male and 60 female CD rats for 104 weeks.

Gross lesions identified at necropsy consisted of liver pallor and thyroid gland enlargement in males dosed at 100 mg/kg/day. The non-neoplastic histopathologic changes associated with treatment included an increased incidence of endometrial hyperplasia, cystic endometrial hyperplasia, and endometrial polyps and polypoid areas in females treated with 100 mg/kg/day. Thyroid changes included an increase in follicular cell adenomas in males (21.7% vs 5.7% in controls) treated with 100 mg/kg/day, and there was follicular carcinoma in one male (1.7%) of this group.

One male rat in the 100 mg/kg/day group (1.7%) and one female rat in the 20 mg/kg/day (1.7%) group had squamous cell carcinomas in the thyroid gland. In the liver, changes included an increase in focal hyperplasia in females treated with 20 (11.7%) or 100 (6.7%) mg/kg/day. Nodular hyperplasias were increased in females treated with 100 mg/kg/day (3.3% vs 1.7% in controls). Hepatocellular carcinoma was found in one decedent female (1.7%) treated with 20 mg/kg/day.

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### **Clinical**

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## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PATIENT MEDICATION INFORMATION

#### FRISIUM® (clobazam tablets)

Read this carefully before you or your child start taking FRISIUM and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FRISIUM.

#### **What is FRISIUM used for?**

FRISIUM is used as add-on therapy in patients whose epilepsy is not well controlled on their current antiepileptic drugs.

#### **How does FRISIUM work?**

FRISIUM belongs to the family of medicines called anticonvulsants. It acts in the brain to block the spread of seizure activity.

#### **What are the ingredients in FRISIUM?**

Medicinal ingredients: clobazam

Non-medicinal ingredients: colloidal silicon dioxide, lactose, magnesium stearate, starch (corn) and talc

#### **FRISIUM comes in the following dosage forms:**

Tablets, 10 mg

#### **Do not use FRISIUM if you or your child:**

- are allergic to the active ingredient clobazam or any of the other ingredients
- have been diagnosed with myasthenia gravis
- have narrow angle glaucoma (increased pressure in your eye)
- have any history of drug or alcohol dependence
- have severe difficulty breathing
- have sleep apnea (pauses in breathing during sleep)
- have severe liver problems
- are in the 1<sup>st</sup> trimester (first 3 months) of pregnancy. Avoid becoming pregnant while taking FRISIUM. Effective birth control methods must be used, Tell your healthcare professional right away if you become pregnant during treatment or plan to get pregnant.
- are breastfeeding. If you are breastfeeding, you should stop before starting treatment with FRISIUM since clobazam passes into breast milk.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you or your child take FRISIUM. Talk about any health conditions or problems you**

**or your child may have, including if you:**

- Have ever had a rash or unusual reaction while taking clobazam or any other antiepileptic drug.
- Are over the age of 65 or debilitated (in a weakened state)
- Have been diagnosed with decreased mental function due to a medical disease
- Use alcohol or drugs. Do not drink alcohol while you are taking FRISIUM.
- Have a history of drug or alcohol abuse. If you are dependent on drugs or alcohol, FRISIUM may increase your dependence.
- Have a history of mental illness, depression, and/or suicide attempts. FRISIUM increases the risk of suicidal thoughts or worsening of depression.
- Have kidney or liver problems. Your healthcare professional may need to adjust the dose.
- Have breathing problems.
- Have muscle weakness and/or spinal /cerebellar ataxia (sudden uncoordinated movements)
- Are pregnant or planning to become pregnant. FRISIUM is **not** to be used in the first trimester of pregnancy and must only be taken in the later stages if your healthcare professional tells you to.
  - If you become pregnant while taking FRISIUM, talk to your healthcare professional about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy. You can enroll in this registry by calling 1-888-233-2334. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.
- Are in labour. Taking FRISIUM immediately before or during childbirth may have an effect on the newborn.
- Have difficulty forming new memories (anterograde amnesia). Anterograde amnesia is known to occur even if antiepileptics are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour.
- Have been taking FRISIUM for a long time. It may not work as well as it used to.
- Are taking birth control.
  - FRISIUM may make hormonal birth control such as “the pill” less effective.
  - Use other forms of safe and effective birth control when taking FRISIUM.
  - You need to use other forms of birth control until the end of your menstrual cycle after stopping treatment.

**Other warnings you should know about:**

- **Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis:** FRISIUM can cause serious skin reactions that can spread to your mouth, lips, face, hands, trunk, arms and legs. These conditions are life-threatening. Stop taking FRISIUM and contact your healthcare professional immediately if you or your child gets a rash or any serious skin reactions. This includes skin peeling, itch, redness, and blisters of the lips, eyes, mouth, nasal passages or genitals. Often, skin reactions occur after 1 to 2 weeks of fever, or other symptoms such as sore throat, fatigue, chills, and headache.



- **Driving and using machines:** Before doing tasks that require special attention, wait until you know how you respond as FRISIUM can cause drowsiness, dizziness and muscle weakness.
- Do not suddenly stop taking FRISIUM. Always follow your healthcare professional's instructions. Stopping this drug quickly may lead to an increase in seizure activity or withdrawal symptoms, such as headaches, trouble sleeping, anxiety, confusion and irritability.

**DURING treatment with FRISIUM, tell your healthcare professional if you or your child develops:**

- Thoughts of suicide or self-harm

**Tell your healthcare professional about all the medicines you or your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with FRISIUM:**

- Hormonal birth control (such as “the pill”).
- Other antiepileptic drugs (such as carbamazepine, phenytoin, valproate, phenobarbital).
- Drugs used to treat fungal infections (such as fluconazole).
- Antidepressant medications (such as fluvoxamine).
- Ticlopidine, used to prevent blood clots and help prevent strokes and heart attacks.
- Omeprazole used to reduce stomach acid.
- Other drugs that affect your nervous system (such as antipsychotics, antihistamines that make you drowsy, anesthetics, other sedatives such as sleeping pills).
- Lithium used to treat bipolar disease.
- Narcotics (strong pain medications). Increased addiction can occur.
- Muscle relaxants and nitrous oxide (products often used in surgery or during dental procedures). FRISIUM can prolong the effects.
- Alcohol.

**How to take FRISIUM:**

FRISIUM is a tablet to be taken by mouth. The tablets can be taken whole, or broken in half along the score line.

Always follow your healthcare professional's instructions. Do not change the prescribed dose yourself. If you think the effect of your medicine is too weak or too strong, talk to your healthcare professional.

**Do not stop taking FRISIUM without talking to your healthcare professional.** Stopping a seizure medicine suddenly can cause serious problems, including seizures that will not stop. Your healthcare professional will tell you if and when you or your child can stop taking this medicine.

If the daily dose of FRISIUM is to be divided, the higher portion should be taken at night (up to 30 mg may be taken as a single dose at night).

If you or your child are taking FRISIUM for an extended period of time, your healthcare professional will perform regular blood tests for liver, kidney and thyroid function.

**Usual dose:**

**Adults:** The starting dose is 5-15 mg/day increasing gradually to a maximum daily dose of 80 mg if needed.

**Children from 2 to 16 years:** The starting dose is 5 mg/day, which can be increased at 5 day intervals to a maximum daily dose of 40 mg/day if needed.

**Infants <2 years:** The dose is based on body weight and will be determined by your healthcare professional.

Elderly patients (>65 years), patients with kidney, liver or breathing problems, muscle weakness or dizziness and unsteadiness when walking (spinal or cerebellar ataxia) and patients who are poor metabolizers of antiepileptic drugs (CYP2C19 poor metabolizers) may require lower doses.

**Overdose:**

If you think you or your child have taken too much FRISIUM, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you or your child have taken too large a dose of FRISIUM, you may become drowsy, confused, and sluggish. You may have trouble walking, reacting, breathing, staying awake, or have low blood pressure. A coma or death is possible. Taking alcohol or other drugs that affect your nervous system at the same time as FRISIUM increases the risk of death. When too much FRISIUM wears off, you could be excited and jittery.

**Missed Dose:**

If you or your child misses a dose of FRISIUM, take it as soon as you remember. If you are close to your next dose, just take your next dose, without making up for the missed dose. Do not take 2 doses at the same time.

**What are possible side effects from using FRISIUM?**

These are not all the possible side effects you or your child may feel when taking FRISIUM. If you or your child experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

**The most common side effects associated with the use of FRISUIM are:**

- Sleepiness/drowsiness, feeling tired/fatigue

- Dizziness

**Common side effects include:**

- Loss of coordination
- Nervousness
- Blurred vision
- Weight increase

**Other side effects include:**

- Headache
- Shakiness, tremor
- Slowed reaction time, muscle weakness
- Confusion, disorientation, trouble speaking, trance, diminished responsiveness
- Constipation, changes in appetite, nausea, vomiting, bloating, dry mouth, trouble swallowing
- Drooling
- Difficulty passing urine, bladder infection
- Fever
- Lower than normal body temperature
- Nasal congestion (blocked nose)
- Rash

The following side effects occur after taking FRISIUM for a long time or at high doses, but they can be reversed: Slowed or slurred speech, unsteady walking and other muscle functions, vision problems, weight gain, and loss of sexual desire.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
Difficulty falling asleep or staying asleep		√	
Psychiatric Disorders (symptoms like irritability, mood swings, restlessness, anxiety, aggressiveness, fits of rage, delusions, changes in thinking)		√	
Nightmares		√	
Hallucinations: See and hear things that are not there		√	
Thoughts of suicide or self-harm			√

Frequent Muscle Spasms		√	
Pneumonia/Aspiration Pneumonia, Bronchitis (symptoms like cough, fever, difficulty breathing, chills)		√	
<b>RARE</b>			
Serious Skin Reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis): Any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages, or genitals. You may also get fever, sore throat, fatigue, chills, headache, cough, body aches or joint pain.			√
<b>VERY RARE</b>			
Allergic reactions: <ul style="list-style-type: none"> <li>• Swelling of lips, eyelids, face, throat, or mouth, accompanied by difficulty in breathing, speaking or swallowing (signs of anaphylactic reactions and angioedema)</li> <li>• Skin rash, fever, swollen glands (swelling of the lymph nodes), and pain in the muscles and joints (signs of hypersensitivity reactions)</li> <li>• Red blotchy rash mainly on face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of systemic lupus)</li> </ul>			√
<b>UNKNOWN</b>			
Altered numbers and types of blood cells (symptoms like unexplained tiredness, weakness, shortness of breath, and sometimes, feeling like you are going to pass out, increased		√ You should tell your healthcare professional who may want to perform a blood	

bruising, nosebleeds, sore throats, or infections)		test	
Anterograde Amnesia (symptoms like loss of the ability to create new memories, inappropriate behaviour)		√	
Respiratory depression (symptoms like shallow slow, weak breathing)			√

If you or your child have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p><b>Reporting Side Effects</b></p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p><b>3 ways to report:</b></p> <ul style="list-style-type: none"> <li>• Online at <a href="http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php">MedEffect</a> (<a href="http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php">http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php</a>);</li> <li>• By calling 1-866-234-2345 (toll-free);</li> <li>• By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> <li>- Fax to 1-866-678-6789 (toll-free), or</li> <li>- Mail to: Canada Vigilance Program Health Canada, Postal Locator 0701E Ottawa, ON K1A 0K9</li> </ul> </li> </ul> <p>Postage paid labels and the Consumer Side Effect Reporting Form are available at <a href="http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php">MedEffect</a> (<a href="http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php">http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php</a>).</p> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

FRISIUM tablets should be stored in their original containers at room temperature, between 15-30°C.

Keep out of reach and sight of children.

**If you want more information about FRISIUM:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](http://hc-sc.gc.ca/index-eng.php) (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer’s website, [www.lundbeck.com](http://www.lundbeck.com), or by calling +1 866 880 4636.

This information is current up to the time of the last revision date shown below, but more current information may be available from the manufacturer.

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