PRODUCT MONOGRAPH

CLOBAZAM - 10

Clobazam Tablets

Pro Doc Standard

10 mg

Anticonvulsant

For Adjunctive Therapy

PRO DOC LTÉE
2925, boul. Industriel
Laval, Quebec
H7L 3W9

DATE OF REVISION:
June 14, 2016

Control #: 194850

NAME OF DRUG

CLOBAZAM - 10

Clobazam Tablets

10 mg

THERAPEUTIC CLASSIFICATION

Anticonvulsant for adjunctive therapy

PART I: HEALTH PROFESSIONAL INFORMATION

ACTIONS

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

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.

Regarding the mechanism of action, it is likely that modifications to the function of gamma-aminobutyric acid (GABA) as an important inhibitory neurotransmitter underlie the pharmacological effects of the benzodiazepines. 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 is enhanced by benzodiazepines, resulting in a decrease in the firing rate of critical neurons in many regions of the brain.

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.

Clobazam is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it has accumulated in white matter and is then redistributed widely. The volume of distribution is large. Approximately 85% to 91% of clobazam is bound to plasma protein.

After oral administration of ^{14}C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. Clobazam is primarily metabolized in the liver. It undergoes dealkylation and hydroxylation before conjugation. Main metabolites found in plasma are N-desmethylclobazam and 4-hydroxyclobazam. Lesser quantities of 4-hydroxy-N-desmethyl clobazam are also found.

N-desmethylclobazam is an active metabolite. After a single dose of 30 mg clobazam, N-desmethylclobazam attains maximum plasma concentrations after 24 - 72 hours. The half-life of N-desmethylclobazam is much longer (mean 42 hours; range 36 - 46 hours) than for that of clobazam (mean 18 hours; range 10 - 30 hours).

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).

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 (see CONTRAINDICATIONS and PRECAUTIONS).

In patients with renal impairment, plasma concentrations of clobazam are reduced, possibly due to impaired absorption of the drug; terminal half-life is largely independent of renal function (see PRECAUTIONS).

There have been no studies that have demonstrated a clear-cut correlation between serum levels of clobazam or of N-desmethylclobazam 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 to 300 ng/mL with the corresponding

range for N-desmethylclobazam being from 1000 to 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-desmethyl-clobazam blood levels are 10 to 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.

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

Bioavailability

A randomized, single dose, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male volunteers. The results obtained from 18 volunteers who completed the study are summarized in the following table. The rate and extent of absorption of clobazam was measured and compared following a single oral dose (2 x 10 mg tablets) of CLOBAZAM (clobazam) 10 mg tablet (Pro Doc Ltée) and Frisium® (clobazam) 10 mg tablet (Hoechst Marion Roussell).

The mean pharmacokinetic parameters of the eighteen subjects completing the study are listed in the following table:

Summary Table of the Comparative Bioavailability Data Clobazam (A single 20 mg dose: 2 x 10 mg tablet) From Measured Data/Fasting Conditions				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)
	Test*	Reference†		
AUC_{72} (ng · hr/mL)	7369.02 7585.4 (24.5)	7271.25 7505.0 (25.5)	101.34%	98 - 105
AUC_{inf} (ng · hr/mL)	8586.73 9077.1 (34.4)	8376.26 8839.5 (33.1)	102.51%	98 - 108
C_{max} (ng/mL)	333.0665 339.025 (18.9)	418.5879 426.272 (19.2)	79.57%	74 - 86
T_{max}§ (h)	2.514 (51.2)	1.597 (65.3)		
$T_{1/2}$§ (h)	25.937 (51.9)	25.026 (47.4)		

*Clobazam (clobazam) 10 mg tablets (for Pro Doc Ltée)
†Frisium® is manufactured by Hoechst Marion Roussel and was purchased in Canada.
§ Expressed as Arithmetic means (CV%) only.

INDICATIONS

CLOBAZAM (clobazam) has been found to be of value as adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

CONTRAINDICATIONS

CLOBAZAM (clobazam) is contraindicated in patients with the following conditions:

- hypersensitivity to clobazam or any of its excipients;
- 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).

WARNINGS

Use in the Elderly

Clobazam 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 ACTIONS and PRECAUTIONS).

Potentiation of Drug Effects

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

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

Physical and Psychological Dependence

Physical and psychological dependence are known to occur in persons taking benzodiazepines. Caution must be exercised if it is at all necessary to administer clobazam to individuals with a history of drug misuse or those who may increase the dose on their own initiative. Such patients must be placed under careful surveillance (see PRECAUTIONS).

As with other benzodiazepines, the therapeutic benefit must be balanced against the risk of habituation and dependence during prolonged use.

A rebound phenomenon or a withdrawal syndrome may follow discontinuation of use of clobazam; thus it should not be abruptly discontinued after prolonged use (see PRECAUTIONS).

Use in Pregnancy, Lactation and Perinatal Period

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. Clobazam 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 clobazam 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.

Nursing mothers in whom therapy with clobazam is indicated should cease breast-feeding, since clobazam passes into breast milk.

Administration of high doses of clobazam 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.

Anterograde Amnesia

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.

Use in Patients with Depression or Psychosis

Clobazam is not recommended for use in patients with depressive disorders or psychosis (see PRECAUTIONS).

Increased risk of pneumonia

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 clobazam, may increase the risk of pneumonia from a decreased ability to manage secretions. The risk of pneumonia increases with the dose level of clobazam (see sections Precautions, Adverse Reactions and Dosage and Administration)

PRECAUTIONS

Driving and Hazardous Activities:

Clobazam 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 clobazam than after other benzodiazepines. Nevertheless, even when used as directed, clobazam 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.

Use in the Elderly

Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to the central nervous system depressant activity of benzodiazepines even after low doses. Manifestations of this central nervous system 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 ACTIONS).

Dependence Liability

Clobazam 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 clobazam over periods of only a few weeks, and applies not only to possible abuse with particularly high doses but also to the therapeutic dose range. The risk of dependence is increased in patients with a history of alcohol or drug abuse. These patients or those who may increase the dose on their own initiative must be closely monitored (see WARNINGS).

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

The rebound phenomenon is characterized by a recurrence in enhanced form of the symptoms which originally led to clobazam treatment (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 clobazam 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, clobazam should be withdrawn gradually (see WARNINGS).

Tolerance

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.

Use in Mental and Emotional Disorders

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, clobazam should not be used in patients suspected of having psychotic tendencies.

Use in Patients with Impaired Renal or Hepatic Function

Clobazam is contraindicated in patients with severe liver dysfunction. In patients with a lesser degree of liver dysfunction, and in patients with renal impairment, responsiveness to clobazam and susceptibility to adverse effects are increased. These patients require low initial doses and gradual dose increments under careful observation (see CONTRAINDICATIONS section and DOSAGE AND ADMINISTRATION section).

Use in Patients with Acute, or Chronic Respiratory Insufficiency

Clobazam can 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 clobazam. Clobazam 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 WARNINGS section, CONTRAINDICATIONS section, ADVERSE REACTIONS section and DOSAGE AND ADMINISTRATION).

Use in Patients with Pre-existing Muscle Weakness or with Spinal or Cerebellar Ataxia

Clobazam can cause muscle weakness. Clobazam 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 CONTRAIDICATIONS sections, and DOSAGE AND ADMINISTRATION section).

Monitoring

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

DRUG INTERACTIONS

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

Most studies of the potential interactions of clobazam with other antiepileptic agents have failed to demonstrate significant interactions with phenytoin, phenobarbital, or carbamazepine. However, 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.

Several of the established antiepileptic agents: carbamazepine, phenytoin, diphenylhydantoin phenobarbital, valproic acid, cause the blood levels of clobazam to decrease slightly. Findings are less consistent with regard to N-desmethylclobazam: serum levels are lower with concurrent valproic acid, but higher with carbamazepine, phenytoin and diphenylhydantoin. Carbamazepine and phenytoin may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethylclobazam.

In summary, if clobazam 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.

Alcohol may also significantly increase plasma clobazam levels (see WARNINGS). Patients should also be cautioned about the possibility of additive effects when clobazam is combined with alcohol or other drugs with central nervous system depressant effects (see CONTRAINDICATIONS and ADVERSE REACTIONS).

Especially when clobazam is administered in higher doses, a mutually potentiating effect is to be expected if other central nervous system depressant drugs (such as antipsychotics, anxiolytics, certain antidepressant agents, anticonvulsant drugs, sedative antihistamines, anesthetics, hypnotics or narcotic analgesics, or other sedatives) are administered or alcohol is consumed at the same time. Special precaution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium (see WARNINGS).

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

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

Toxicologic Studies

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 CARCINOGENICITY section). The relevance of these findings to man has not been established.

ADVERSE REACTIONS

From 19 published studies of clobazam 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%]) while other effects occurred at a less than 1% incidence.

Clobazam may cause sedation leading to tiredness and sleepiness, especially at the beginning of treatment with clobazam and when higher doses are used. Slowing of reaction time, drowsiness, numbed emotions, confusion, headaches, dryness of the mouth, constipation, loss of appetite, nausea, dizziness, muscle weakness, ataxia, disorientation, or a fine tremor of the fingers may occur.

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 clobazam must be discontinued.

Tolerance and dependence may develop, especially during prolonged use.

Reports have been received of Stevens - Johnson syndrome (SJS), including toxic epidermal necrolysis (TEN).

Isolated cases of skin reactions such as rashes, exanthema or urticaria have been observed in very rare cases.

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 behavior.

Clobazam 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 clobazam. In a 15 weeks Lennox-Gastaut Syndrome Placebo Controlled Trial, the frequency of pneumonia increased from 2% in placebo group, up to 7 % in clobazam-exposed patients with a maximum daily dose of 20 mg for ≤ 30 kg/body weight; 40 mg for › 30 kg/body weight.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdose and intoxication with benzodiazepines - including clobazam - 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. 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 clobazam. Secondary elimination of clobazam, by forced diuresis or hemodialysis, is ineffective. 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 immediately.

DOSAGE AND ADMINISTRATION

Adults

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

Children

In infants (<2 years), the initial daily dose is 0.5-1 mg/kg/day. The initial dose in children (2-16 years) should be 5 mg/day, which may be increased at 5-day intervals to a maximum of 40 mg/day.

Patients with Impaired Liver or Renal Function

CLOBAZAM (clobazam) should be used at a reduced dosage in these patients.

Use in patients with acute, or chronic respiratory insufficiency

In patients with lesser degree of acute or chronic, respiratory insufficiency, respiratory function should be monitored and a dose reduction of CLOBAZAM (clobazam) may be necessary. (See sections: Warnings, Precautions, and Adverse Reactions)

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 CLOBAZAM (clobazam) may be necessary.

Administration

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.

As with all benzodiazepines, abrupt withdrawal may precipitate seizures. It is therefore recommended that CLOBAZAM (clobazam) be gradually reduced in dose before treatment is discontinued.

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

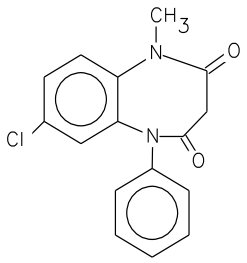
PART II: SCIENTIFIC INFORMATION

DRUG SUBSTANCE

Proper Name: Clobazam (INN)

Chemical Names:
1) 7-chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4-(3*H*,5*H*) dione;
2) 1*H*-1,5-Benzodiazepine-2,4-(3*H*,5*H*)-dione, 7-chloro-1-methyl-5-phenyl-.

Structural Formula:



Molecular Formula: $C_{16}H_{13}ClN_2O_2$

Molecular Weight: 300.75

Description:

White, crystalline powder. Slightly soluble in water, ethanol (96%) and methanol. Melting range is between 179.0° - 185.0°C.

COMPOSITION

CLOBAZAM - 10 (clobazam) Tablets contain 10 mg of clobazam. CLOBAZAM Tablets also contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate (spray-dried), magnesium stearate, microcrystalline cellulose (PH 102).

STABILITY AND STORAGE CONDITIONS

CLOBAZAM Tablets should be stored at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORM

CLOBAZAM - 10 Tablet 10 mg:

Each round, white, biconvex tablet, scored and engraved "CLO" over "10" on one side, plain on the other, contains 10 mg of clobazam. Available in bottles of 30, 100 and 250, unit dose packages of 30 and 100, and Long-Term Care unit dose packages (LTC paks) of 620 and 700 tablets.

PHARMACOLOGY

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 were 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 1).

Table 1
Anticonvulsant Activity of Antiepileptic Drugs in Mice (chemically induced seizures)
(ED_{50} [mg/kg orally])

	Pentetrazol 125 mg/kg	Picrotoxin 15 mg/kg	Bicuculline 5 mg/kg	Isoniazid 600 mg/kg	Nicotine 1.5 mg/kg	Strychnine 1.2 mg/kg
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_{50} 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_{50}/ED_{50} where the TD_{50} 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 2).

Table 2
Protective Indices of Clobazam and Other Antiepileptics in Tests on Anticonvulsant Activity in Mice

	Electro-convulsive Seizures	Pentetrazol (tonic)	Pentetrazol (clonic)	Picrotoxin	Bicuculline	Isoniazid	Nicotine	Strychnine
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.

Clobazam is extensively metabolized and is not excreted in unchanged form by any species studied. For serum concentrations between 0.05 and 10 μg/mL, the binding to serum proteins is shown in Table 3.

Table 3
Binding of ^{14}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

After oral administration, absorption of clobazam was practically complete in all three animal species. Data are given in Table 4 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 4
Blood Levels after Oral Administration of ^{14}C-labelled Clobazam

Species	n	Maximum Total Concentration (Φg/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

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 5). Elimination was almost completed after 48 hours in all species.

Table 5 Excretion after Administration of ^{14}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	102 ± 3
Monkey	Orally	2.5	61 ±14	N.D.	

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.

In several studies clobazam exhibited activity against seizures with doses usually ranging below those that cause disorders in motor activity (see ACTIONS section and Table 2). This separation is evident also with N-desmethylclobazam. 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 tranquillizing 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_{50} 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_{50} was 6000 mg/kg, the intraperitoneal LD_{50}, 740-1526 mg/kg, and the subcutaneous toxicity, >5000 mg/kg. In rabbits, the oral LD_{50} 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 tremors, 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-desmethylclobazam 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.

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/days. 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).

Teratologic studies were performed in mice, rats and thalidomide-sensitive rabbits treated in the diet with clobazam at doses of up to 400 mg/kg of body weight/day.

In rats and mice, no teratogenic effects were noted. In the fetuses and in the neonatal animals, there were no differences between the test groups and the control group with regard to number of implantations, resorptions, number of live and dead fetuses, placental weight, crown-rump length of fetuses, and sex ratio in the live fetuses, nor were there any external, visceral or skeletal malformations or anomalies attributable to clobazam. In the reared fetuses of the dams treated with clobazam during pregnancy, no retardation in post-natal growth and no external malformations and no visceral or skeletal abnormalities were observed except for four cases of cleft palate occurring at a dose of 100 mg/kg/day.

In rabbits, the rate of fetal resorption was higher in animals treated with 100 mg/kg than in the controls. In the group treated with 4 mg/kg, one unilateral exophthalmus, one exencephalus combined with ceolosomy and syndactyly of the front legs were observed, whilst in the 20 mg/kg group, one hydrocephalus with umbilical hernia was noted; these malformations were thought not to be drug related.

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 groups 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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PART III: CONSUMER INFORMATION[1]

CLOBAZAM - 10
(clobazam tablets)

This leaflet is part III of a three-part "Product Monograph" published when CLOBAZAM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CLOBAZAM. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Add-on therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy.

What it does:
CLOBAZAM is an antiepileptic drug which can be used with other anticonvulsant drugs to manage epileptic seizures.

When it should not be used:
CLOBAZAM should not be used under the following conditions:

- If you are allergic to clobazam or any of its other ingredients
- If you have been diagnosed with myasthenia gravis
- If you have narrow angle glaucoma
- If you have any history of drug or alcohol dependence
- If you have severe difficulty breathing
- If you have sleep apnea (pauses in breathing during sleep)
- If you have severe liver or kidney disease
- During 1st trimester of pregnancy and breast-feeding.

What the medicinal ingredient is:
Clobazam is the active ingredient.

What the non-medicinal ingredients are:

- Colloidal silicon dioxide
- Lactose monohydrate (spray-dried)
- Magnesium stearate
- Croscarmellose sodium
- Microcyrstalline cellulose |(PH 102)

What dosage forms it comes in:
Tablet 10 mg.

WARNINGS AND PRECAUTIONS

BEFORE you use CLOBAZAM, talk to your doctor or pharmacist if you:

- Are elderly or debilitated
- Have been diagnosed with decreased mental function due to a medical disease
- Use alcohol or drugs with central nervous system (CNS) depressant effects
- Have a history of drug misuse or you may increase medication doses on your own. If you are dependent on drugs or alcohol, CLOBAZAM may increase your dependence.
- Have mental or emotional disorders such as suicidal tendencies. CLOBAZAM is not recommended in patients with a diagnosis of depression or psychosis (mental illness).
- Have kidney or liver disease
- Have sudden or ongoing difficulty breathing that is not severe
- Already have muscle weakness and/or spinal /cerebellar ataxia (sudden uncoordinated movements.
- Are pregnant, CLOBAZAM is harmful to an unborn child if used during the first trimester of pregnancy. Avoid becoming pregnant. Effective birth control methods should be used. Tell your doctor right away if you become pregnant during treatment or plan to get pregnant.

1 FRISIUM product monograph, Aventis Pharma Inc., pages 27-32.

- Are breast feeding. If you have been nursing, you should stop before starting treatment with CLOBAZAM since clobazam passes into breast milk. Ask your baby's doctor to recommend a formula that would be best for your baby.
- Are immediately before or during childbirth because CLOBAZAM may have an effect on the newborn.
- Do not drive, operate dangerous machinery or engage in other dangerous activities, as CLOBAZAM may cause impairment of your alertness. Be sure you are not suffering from drowsiness, dizziness or muscle weakness before you resume these activities.
- Difficulty in forming new memories (anterograde amnesia) is known to occur even if anti- anxiety medications (benzodiazepines) are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behavior.

Do not drink alcohol if you are taking CLOBAZAM.

Like other medications in this class, use of CLOBAZAM may lead to a need so strong that it becomes necessary to have CLOBAZAM to function properly (addiction).

Do not suddenly stop taking CLOBAZAM. Always follow your doctor's instructions. Stopping this drug quickly may lead to a rebound phenomenon (seizures) or withdrawal symptoms, such as headaches, trouble sleeping, anxiety, confusion, irritability.

Reports of aspiration pneumonia and pneumonia have been reported with clobazam.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about any medication that you are taking or plan to take including any medicine obtained without a prescription, vitamin or mineral supplement, and natural health products.

When CLOBAZAM is given with other drugs that control epilepsy, your doctor may need to adjust the CLOBAZAM dosage.

If CLOBAZAM is given in higher doses with other CNS depressant drugs (such as antipsychotics, certain antidepressant agents, anticonvulsant drugs, antihistamines with drowsy effects, anesthetics, hypnotics or narcotic pain medication, other sedatives or alcohol), it may increase the effects of these medications including CLOBAZAM. Special precautions must be taken when taking CLOBAZAM and lithium. Your doctor may need to monitor these interactions with blood tests.

If CLOBAZAM is used with narcotic pain medications, increased psychological dependence (addiction) can occur.

CLOBAZAM can prolong the effect of muscle relaxants and nitrous oxide (products often used in surgery or during dental procedures).

PROPER USE OF THIS MEDICATION

Usual Dose:

CLOBAZAM is a tablet to be taken by mouth. Always follow your doctor'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 doctor. Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms or seizures.

Adults should take small doses of CLOBAZAM initially (5-15 mg/day) gradually increasing to no more than 80 mg/day, as needed.

Infants less than 2 years should take an initial dose of 0.5-1 mg/kg/day.
Children 2-16 years should initially take 5 mg/day, increasing to no more than 40 mg/day in 5- day intervals.

Patients with kidney or liver disease should be given a lower dose.

If the daily dose of CLOBAZAM 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). Always follow your doctor's instructions.

If your doctor prescribes repeated cycles of CLOBAZAM, your doctor should perform periodic tests for liver, kidney and thyroid function.

Overdose:

Contact your doctor, Regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your CLOBAZAM. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show your doctor your bottle of tablets.

If you are given too large a dose of CLOBAZAM, you may become drowsy, confused, and sluggish. You may have trouble breathing, staying awake, or have low blood pressure. A coma is possible. Taking alcohol or other CNS depressant medications at the same time as CLOBAZAM could lead to death. When too much CLOBAZAM wears off, you could be excited and jittery.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of CLOBAZAM, 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like most medicines, besides the beneficial effects, CLOBAZAM can have side effects. If you experience any of the following side effects, call your doctor right away.

The most often reported side effects in patients with epilepsy who are taking CLOBAZAM are drowsiness, dizziness and tiredness. Some of these patients stopped treatment because of these side effects. These side effects did not occur as often in patients under 16 years of age as they did in adult patients, however, these patients stopped treatment as often as adult patients because of the side effects.

Common side effects include:

- Loss of muscle coordination
- Dizziness
- Behavior disorders
- Blurred vision
- Nervousness
- Hostility

Other side effects include:

- Tiredness and sleepiness (especially at the start of your treatment with CLOBAZAM, and at higher doses)
- Slowing reaction time
- Drowsiness
- Numbed emotions
- Confusion
- Headaches
- Mouth dryness
- Various stomach problems (constipation, loss of appetite, nausea)
- Muscle weakness
- Disorientation
- Slight shaking of the fingers
- Sudden or ongoing difficulty breathing
- Pneumonia or aspiration pneumonia cough, fever, chills

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

It is possible that you may not feel the effects of CLOBAZAM or may come to depend on CLOBAZAM if you are taking it for a long time.

Withdrawal-related Side Effects
Stopping this drug quickly may lead to seizures or withdrawal symptoms, such as headaches, trouble sleeping, anxiety, confusion, irritability.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom/effect		Talk to your doctor or pharmacist		Stop taking drug and seek immediate emergency treatment
		Only if severe	In all cases	
Common	Difficulty falling asleep or sleeping through†		✓	
	Irritability†		✓	
	Increased restlessness, irritation, and/or mood swings associated with mental tension (Acute agitational state)†		✓	
	Anxiety†		✓	
	Aggressiveness†		✓	
	Unfounded ideas that can be related to suspicions or paranoid thoughts, self-importance, illness, self-blame, or hopelessness (Delusion†)		✓	
	Fits of Rage†		✓	
	Nightmares†		✓	
	See and hear things that are not there (Hallucinations†)		✓	
	Severe mental disorders that cause abnormal thinking and perceptions (Psychotic reactions†)		✓	
	Suicidal Tendencies†			✓
	Frequent Muscle Spasms†			✓
	Cough, fever, difficulty breathing		✓	
Uncommon	A rare, serious disorder in which your skin and mucous membranes react severely to a medication (Stevens-Johnson syndrome [SJS])			✓

	Severe skin reaction where the upper surface of your skin detaches like a patient who has suffered bums (Toxic Epidermal Necrolysis [TEN])			✓
Very rare	Allergic reactions: • Swelling of lips, eyelids, face, throat, or mouth, accompanied by difficulty in breathing, speaking or swallowing (signs of anaphylactic reactions and angioedema) • Skin rash, fever, swollen glands (swelling of the lymph nodes), and pain in the muscles and joints (signs of hypersensitivity reactions) • Blistering of the skin and/or mucous membranes of the lips, eyes, mouth, nasal passage or genitals (signs of serious skin reaction) • Red blotchy rash mainly on face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of systemic lupus)			✓

† Opposite reactions may occur, especially in children and the elderly. In the event of such reactions, treatment with CLOBAZAM must be discontinued.

This is not a complete list of side effects. For any unexpected side effects while taking

CLOBAZAM, contact your doctor or pharmacist

HOW TO STORE IT

CLOBAZAM tablets should be stored at room temperature, between 15-30°C (59-86°F).

IMPORTANT: PLEASE READ

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator: 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or info@prodoc.qc.ca.

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