PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

APO-CLOBAZAM

Clobazam

Tablets, 10 mg

Apotex Standard

Prescribed Antiepileptic

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T9

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APO-CLOBAZAM
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10 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Oral	Tablet - 10 mg	colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate (spray-dried), magnesium stearate, microcrystalline cellulose (PH 102).

INDICATIONS AND CLINICAL USE

APO-CLOBAZAM (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 clobazam in adults aged 65 and over has not been established (see WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY sections).

Long-term use of APO-CLOBAZAM should be avoided in elderly patients. Enhanced monitoring is recommended (see WARNINGS AND PRECAUTIONS, Falls and fractures; DOSAGE AND ADMINISTRATION, Dosing considerations).

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).

Serious Warnings and Precautions

Addiction, Abuse and Misuse
The use of benzodiazepines, including APO-CLOBAZAM, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing APO-CLOBAZAM
- Monitor all patients regularly for the development of these behaviours or conditions.
- APO-CLOBAZAM should be stored securely to avoid theft or misuse.

Withdrawal
Benzodiazepines, like APO-CLOBAZAM, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of APO-CLOBAZAM.
- Terminate treatment with APO-CLOBAZAM by gradually tapering the dosage schedule under close monitoring.

(see WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant use with Opioids
Concomitant use of APO-CLOBAZAM and opioids may result in profound sedation, respiratory depression, coma and death (see WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

WARNINGS AND PRECAUTIONS

General
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 CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION sections).

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 levels of clobazam 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, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections).

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.

Concomitant use with opioids:
Concomitant use of benzodiazepines, including APO-CLOBAZAM, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; DRUG INTERACTIONS, Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe APO-CLOBAZAM concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of APO-CLOBAZAM than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking APO-CLOBAZAM, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when APO-CLOBAZAM is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

Dependence/Tolerance
Use of benzodiazepines, such as APO-CLOBAZAM, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with APO-CLOBAZAM with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing APO-CLOBAZAM. In individuals prone to substance use disorder, APO-CLOBAZAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- APO-CLOBAZAM should always be prescribed at the lowest effective dose for the shortest duration possible.

- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

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.

Withdrawal:
Benzodiazepines, such as APO-CLOBAZAM, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal signs and symptoms should seek immediate medical attention.

(see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; DOSAGE AND ADMINISTRATION, Dosing Considerations)

Hepatic/Biliary/Pancreatic

Clobazam is contraindicated in patients with severe liver dysfunction. In patients with a lesser degree of liver dysfunction (mild to moderate hepatic 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, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY sections). In long-term treatment, hepatic function must be checked regularly.

Musculoskeletal

Falls and fractures:

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Neurologic

In clinical trials, somnolence or sedation was reported at all effective doses, especially at the beginning of treatment with clobazam 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 clobazam 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 behaviour 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, clobazam should not be used in patients suspected of having psychotic tendencies.

Clobazam 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_{max}) 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 clobazam in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable. In long-term treatment, renal function must be checked regularly.

Respiratory
Clobazam 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 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 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 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 ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

Skin
Serious, potentially life-threatening skin reactions, including Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing period. Patients should be closely monitored for signs or symptoms of DRESS and SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. These commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. APO-Clobazam should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest DRESS or SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered. (see ADVERSE REACTIONS, Post-Market Reactions).

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. 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.

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 clobazam is indicated should cease breast-feeding, since clobazam passes into breast milk.

Geriatrics (> 65 years of age):
Long-term use of APO-CLOBAZAM should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

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 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 clobazam 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 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%]).

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

Post-Market Adverse Reactions

Skin and subcutaneous tissue disorders:
Rash, urticaria, exanthema, Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS), Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN).

Injury, Poisoning and Procedural Complications:
There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal:
Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as APO-CLOBAZAM. Severe and life-threatening symptoms have been reported. (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Additional Explanatory Information for Post-Market Adverse Drug Reactions

Clobazam 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 clobazam 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.

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 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 ≤ 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[a] N=58 %	Medium[b] N=62 %	High[c] N=59 %	
Gastrointestinal Disorders					
Vomiting	5	9	5	7	7
Constipation	0	2	2	10	5
Dysphagia	0	0	0	5	2
General Disorders and Administration Site Conditions					
Pyrexia	3	17	10	12	13
Irritability	5	3	11	5	7
Fatigue	2	5	5	3	5
Infections and Infestations					
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
Metabolism and Nutrition Disorders					
Decreased appetite	3	3	0	7	3
Increased appetite	0	2	3	5	3
Nervous System Disorders					
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
Psychiatric Disorders					
Aggression	5	3	8	14	8
Insomnia	2	2	5	7	5
Respiratory Disorders					
Cough	0	3	5	7	5
Nasal congestion	2	5	0	2	2
Skin and Subcutaneous Tissue Disorders					

	Placebo N=59 %	Clobazam Dose Level			All Clobazam N=179 %
		Low[a] N=58 %	Medium[b] N=62 %	High[c] N=59 %	
Rash	3	2	3	5	3

[a]0.25 mg/kg/day; tablets; orally; for 15-18 weeks
[b]0.5 mg/kg/day; tablets; orally; for 15-18 weeks
[c]1.0 mg/kg/day; tablets; orally; for 15-18 weeks

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

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of APO-CLOBAZAM and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see WARNINGS AND PRECAUTIONS , General, Risks from Concomitant use with Opioids)

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 clobazam.

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 clobazam.

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.

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

Clobazam	Ref	Effect	Clinical comment
Carbamazepine, phenytoin, phenobarbital, valproate	CT	Caused the blood levels of clobazam to decrease slightly With regard to N-desmethylclobazam: 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-desmethylclobazam: 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-desmethylclobazam, 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 clobazam 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 administrated 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

- APO-CLOBAZAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- APO-CLOBAZAM can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure. (see WARNINGS AND PRECAUTIONS section).
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of APO-CLOBAZAM should be avoided in elderly patients. Enhanced monitoring is recommended.
- 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**: APO-CLOBAZAM (clobazam) 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 APO-CLOBAZAM (clobazam) 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 APO-CLOBAZAM (clobazam) 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 ≤ 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-desmethylclobazam, 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 APO-CLOBAZAM (clobazam) 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 APO-CLOBAZAM (clobazam), 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 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 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 clobazam. 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 $GABA_{A\alpha 2}$ 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-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 ng - 300 ng/mL with the corresponding range for N-desmethylclobazam 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-desmethylclobazam 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-desmethylclobazam is approximately 80-90% and 70%, respectively.

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

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

Excretion: After oral administration of ^{14}C-labelled clobazam to man, approximately 90% of the radioactivity was recovered in urine. The half-life of N-desmethylclobazam is much longer (mean 42hours; 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

APO-CLOBAZAM tablets should be stored at room temperature 15°C-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.

APO-CLOBAZAM Tablet 10 mg:

Each round, white, biconvex tablet engraved "APO" on one side, scored and engraved "CLO" over "10" on the other, contains 10 mg of clobazam. Available in unit dose packages of 30.

Composition

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

PART II: SCIENTIFIC INFORMATION

PHARMCEUTICAL INFORMATION

Drug Substance

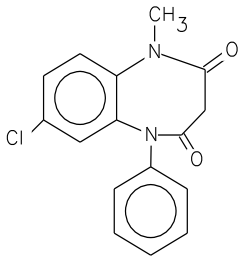
Proper name: Clobazam (INN)

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-.

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

Molecular weight: 300.75 g/mol

Structural formula:



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

CLINICAL TRIALS

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.

Comparative Bioavailability Studies

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 APO-CLOBAZAM (clobazam) 10 mg tablet (Apotex Inc.) 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)		
*APO–CLOBAZAM (clobazam) 10 mg tablets (Apotex Inc. previously Novex Pharma) †Frisium® is manufactured by Hoechst Marion Roussel and was purchased in Canada. § Expressed as Arithmetic means (CV%) only.				

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-desmethylclobazam showed weak inhibition of CYP2C9, UGT1A4, UGT1A6 and UGT2B4.

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

Clobazam and N-desmethylclobazam 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-desmethylclobazam, 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-desmethylclobazam. Compared to CYP2C19 extensive metabolizers, N-desmethylclobazam 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 3).

Table 3 - 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 4).

Table 4 - 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.

Pharmacokinetics - Animal Data

Absorption

After oral administration, absorption of clobazam was practically complete in all three animal species. Data are given in Table 5 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 5 - Blood levels after oral administration of ^{14}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 6.

Table 6 - 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

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

Table 7 - 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	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 4). 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 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_{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 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-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.

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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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

APO-CLOBAZAM
(clobazam tablets)

Read this carefully before you or your child start taking APO-CLOBAZAM 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 APO-CLOBAZAM.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take APO-CLOBAZAM as prescribed, you are at risk for abuse, misuse and addiction. This can result in overdose or death, especially if it is taken with:

- **opioids**
- **alcohol or**
- **illicit drugs**

Your doctor should:

- **talk to you about the risks of treatment with APO-CLOBAZAM as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing APO-CLOBAZAM**
- **monitor you while you are taking APO-CLOBAZAM for the signs and symptoms of misuse and abuse. If you feel like you are craving APO-CLOBAZAM, or not using it as directed, talk to your doctor right away.**

Store APO-CLOBAZAM in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking APO-CLOBAZAM, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)

- **Always contact your doctor before stopping, or lowering your dose of APO-CLOBAZAM or changing your medicine.**

APO-CLOBAZAM with Opioids: Taking APO-CLOBAZAM with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**
- **coma**
- **death**

What is APO-CLOBAZAM used for?
APO-CLOBAZAM is used as add-on therapy in patients whose epilepsy is not well controlled on their current antiepileptic drugs.

If you are 65 years or older, talk to your doctor before starting APO-CLOBAZAM. APO-CLOBAZAM may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does APO-CLOBAZAM work?
APO-CLOBAZAM 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 APO-CLOBAZAM?
Medicinal ingredients clobazam
Non-medicinal ingredients: colloidal silicon dioxide, lactose monohydrate (spray-dried), magnesium stearate, croscarmellose sodium, microcrystalline cellulose (PH102)

APO-CLOBAZAM comes in the following dosage forms:
Tablets, 10 mg.

Do not use APO-CLOBAZAM 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 1st trimester (first 3 months) of pregnancy. Avoid becoming pregnant while taking APO-CLOBAZAM. 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 APO-CLOBAZAM 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 APO-CLOBAZAM. 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 APO-CLOBAZAM.
- Have a history of drug or alcohol abuse. If you are dependent on drugs or alcohol, APO-CLOBAZAM may increase your dependence.
- Have a history of mental illness, depression, and/or suicide attempts. APO-CLOBAZAM 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. APO-CLOBAZAM 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 APO-CLOBAZAM 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 APO-CLOBAZAM 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 APO-CLOBAZAM for a long time. It may not work as well as it used to.
- Are taking birth control

    - APO-CLOBAZAM may make hormonal birth control such as “the pill” less effective.
    - Use other forms of safe and effective birth control when taking APO-CLOBAZAM.
    - You need to use other forms of birth control until the end of your menstrual cycle after stopping treatment.
- have ever had a problem with:
    - substance use, including prescribed or illegal drugs, or
    - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

Other warnings you should know about:

Severe Skin Reactions:
APO-CLOBAZAM can cause serious life-threatening skin reactions, such as:

- Stevens-Johnson syndrome (SJS),
- Toxic Epidermal Necrolysis (TEN) and
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

These skin reactions can spread to your mouth, lips, face, hands, trunk (torso), arms and legs. Stop taking APO-CLOBAZAM and contact your healthcare professional right away if you or your child experiences:

- fever
- severe rash
- peeling skin
- swollen lymph glands
- flu-like feeling
- yellow skin or eyes
- shortness of breath
- dry cough
- chest pain or discomfort
- feeling thirsty
- urinating less often, less urine

- **Driving and using machines:** Before doing tasks that require special attention, wait until you know how you respond as APO-CLOBAZAM can cause drowsiness, dizziness and muscle weakness.
- Do not suddenly stop taking APO-CLOBAZAM. 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.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop APO-CLOBAZAM.

Your risk of going through withdrawal is higher if you are taking APO-CLOBAZAM for a long time or at high doses. However, symptoms can still occur if you are taking APO-CLOBAZAM as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behaviour and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always contact your doctor before stopping or reducing your dose of APO-CLOBAZAM or changing medications
- always follow your doctor's instructions on how to reduce your dose carefully and safely
- tell your doctor **right away** if you experience any unusual symptoms after changing or stopping your treatment

APO-CLOBAZAM with Opioids: Taking APO-CLOBAZAM with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking APO-CLOBAZAM

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and APO-CLOBAZAM affects you.

Falls and Fractures: Benzodiazepines like APO-CLOBAZAM can cause you to feel sleepy, dizzy and affect your balance. This increases the risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

DURING treatment with APO-CLOBAZAM, 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.

Serious Drug Interactions
Taking APO-CLOBAZAM and opioids may cause: • **severe drowsiness** • **trouble breathing** • **coma** • **death**

The following may interact with APO-CLOBAZAM:

- 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). APO-CLOBAZAM can prolong the effects.
- Alcohol.

How to take APO-CLOBAZAM

APO-CLOBAZAM 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.

Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor’s instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Do not stop taking APO-CLOBAZAM 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 APO-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).

If you or your child are taking APO-CLOBAZAM 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 APO-CLOBAZAM, 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 APO-CLOBAZAM, 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 APO-CLOBAZAM increases the risk of death. When too much APO-CLOBAZAM wears off, you could be excited and jittery.

Missed Dose:

If you or your child misses a dose of APO-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.

What are possible side effects from using APO-CLOBAZAM?

These are not all the possible side effects you or your child may feel when taking APO-CLOBAZAM. 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 APO-CLOBAZAM 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
- Falls and fractures

The following side effects occur after taking APO-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 problems, weight gain, and loss of sexual desire.

Serious side effects and what to do about them

	Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
COMMON				
	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).		✓	
RARE				
	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.			✓
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) • Red blotchy rash mainly on face which may be accompanied by fatigue, fever, nausea, loss of appetite (signs of systemic lupus)			✓
UNKNOWN				
	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 bruising, nosebleeds, sore throats, or infections)		✓ You should tell your healthcare professional who may want to perform a blood test	
	Anterograde Amnesia (symptoms like loss of the ability to create new memories, inappropriate behaviour)		✓	
	Respiratory depression (symptoms like shallow, slow, weak breathing)			✓
	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (serious skin reaction that may affect more than one organ): fever, severe rash, peeling skin, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine			✓

Serious side effects and what to do about them				
Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.		✓	

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.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

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

Keep out of reach and sight of children.

If you want more information about APO-CLOBAZAM:

- 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); the manufacturer's website, http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet can also be found at: http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

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