640-2018-09

CLOBAZAM tablets,
for oral use, CIV
2050284

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLOBAZAM TABLETS safely and effectively. See full prescribing information for CLOBAZAM TABLETS.

CLOBAZAM tablets, for oral use, CIV
Initial U.S. Approval: 2011

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

See full prescribing information for complete boxed warning.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death (5.1, 7.1).
- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

----------INDICATIONS AND USAGE----------

Clobazam is a benzodiazepine indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older (1)

----------DOSAGE AND ADMINISTRATION----------

- For doses above 5 mg/day administer in two divided doses (2.1)
- Patients ≤30 kg body weight: Initiate at 5 mg daily and titrate as tolerated up to 20 mg daily (2.1)
- Patients >30 kg body weight: Initiate at 10 mg daily and titrate as tolerated up to 40 mg daily (2.1)
- Dosage adjustment needed in following groups:
  - o Geriatric patients (2.4, 8.5)
  - o Known CYP2C19 poor metabolizers (2.5)
  - o Mild or moderate hepatic impairment; no information for severe hepatic impairment (2.7, 8.8)
- Reduce dose, or discontinue drug gradually (2.2)
- Tablets: Administer whole, broken in half along the score, or crush and mix in applesauce (2.3)
- Tablets: Can be taken with or without food (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet: 10 mg and 20 mg with a functional score (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity to the drug or its ingredients (4)

----------WARNINGS AND PRECAUTIONS----------

- Somnolence or Sedation: Monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of other CNS depressants (5.2, 5.3)
- Withdrawal: Symptoms may occur with rapid dose reduction or discontinuation. Discontinue clobazam tablets gradually (5.4)
- Serious Dermatological Reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis): Discontinue clobazam tablets at first sign of rash unless the rash is clearly not drug-related (5.5)
- Physical and Psychological Dependence: Monitor patients with a history of substance abuse for signs of habituation and dependence (5.6, 9)
- Suicidal Behavior and Ideation: Monitor for suicidal thoughts or behaviors (5.7)

----------ADVERSE REACTIONS----------

Adverse reactions that occurred at least 10% more frequently than placebo in any clobazam dose included constipation, somnolence or sedation, pyrexia, lethargy, and drooling (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Alcohol: Increases blood levels of clobazam by about 50% (7.2)
- Drugs metabolized by CYP2D6: Lower doses of these drugs may be required when used concomitantly with clobazam tablets (7.3)
- Strong or Moderate CYP2C19 Inhibitors: Dosage adjustment of clobazam may be necessary (7.4)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.1), Drug Interactions (7.1)*].
- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

Clobazam tablet is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

A daily dose of clobazam tablets greater than 5 mg should be administered in divided doses twice daily; a 5 mg daily dose can be administered as a single dose. Dose patients according to body weight. Individualize dosing within each body weight group, based on clinical efficacy and tolerability. Each dose in Table 1 (e.g., 5 mg to 20 mg in ≤30 kg weight group) has been shown to be effective, although effectiveness increases with increasing dose *[see Clinical Studies (14)]*. Do not proceed with dose escalation more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.

Table 1. Recommended Total Daily Dosing by Weight Group

	≤30 kg Body Weight	>30 kg Body Weight
Starting Dose	5 mg	10 mg
Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

2.2 Gradual Withdrawal

As with all antiepileptic drugs and benzodiazepines, withdraw clobazam tablets gradually. Taper by decreasing the total daily dose by 5 mg to 10 mg/day on a weekly basis until discontinued *[see Warnings and Precautions (5.4)]*.

2.3 Important Administration Instructions

Clobazam Tablet Oral Administration

Clobazam tablets can be taken with or without food.

Clobazam tablets can be administered whole, broken in half along the score, or crushed and mixed in applesauce.

2.4 Dosage Adjustments in Geriatric Patients

Plasma concentrations at any given dose are generally higher in the elderly: proceed slowly with dose escalation. The starting dose should be 5 mg/day for all elderly patients. Then titrate elderly patients according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on weight) may be started on day 21 *[see Use in Specific Populations (8.5)]*.

2.5 Dosage Adjustments in 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 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, an additional titration to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group) may be started on day 21 *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.5)]*.

2.6 Patients with Renal Impairment

No dose adjustment is required for patients with mild and moderate renal impairment. There is no experience with clobazam tablets 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 *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

2.7 Dosage Adjustments in Patients with Hepatic Impairment

Clobazam tablet is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam tablets. For this reason, proceed slowly with dosing escalations. For patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9), the starting dose should be 5 mg/day in both weight groups. Then titrate patients according to weight, but to half the dose presented in Table 1, as tolerated. If necessary and based upon clinical response, start an additional titration on day 21 to the maximum dose (20 mg/day or 40 mg/day, depending on the weight group). There is inadequate information about metabolism of clobazam tablets in patients with severe hepatic impairment. Therefore no dosing recommendation in those patients can be given *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg and 20 mg with a functional score for oral administration.

Clobazam tablets, 10 mg are white to off white, oval tablets debossed 'C' and '9' along with functional score on one side and 'H' on the other side.

Clobazam tablets, 20 mg are white to off white, oval tablets debossed 'C' and '13' along with functional score on one side and 'H' on the other side.

4 CONTRAINDICATIONS

Clobazam tablet is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients. Hypersensitivity reactions have included serious dermatological reactions *[see Warnings and Precautions (5.5)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including clobazam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe clobazam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when clobazam is used with opioids *[see Drug Interactions (7.1)].*

5.2 Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants

Since clobazam has a central nervous system (CNS) depressant effect, patients or their caregivers should be cautioned against simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Drug Interactions (7.2)]*.

5.3 Somnolence or Sedation

Clobazam causes somnolence and sedation. In clinical trials, somnolence or sedation was reported at all effective doses and was dose-related.

In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system depressants. 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.

5.4 Withdrawal Symptoms

Abrupt discontinuation of clobazam tablets should be avoided. Clobazam tablets should be tapered by decreasing the dose every week by 5 mg to 10 mg/day until discontinuation *[see Dosage and Administration (2.2)]*.

Withdrawal symptoms occurred following abrupt discontinuation of clobazam tablets; the risk of withdrawal symptoms is greater with higher doses.

As with all antiepileptic drugs, clobazam tablets should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.

Withdrawal symptoms (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, and anxiety) have been reported following abrupt discontinuance of benzodiazepines. The more severe withdrawal symptoms have usually been limited to patients who received excessive doses over an extended period of time, followed by an abrupt discontinuation. Generally milder withdrawal symptoms (e.g., dysphoria, anxiety, and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic doses for several months.

5.5 Serious Dermatological Reactions

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the postmarketing period. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment initiation or when re-introducing therapy. Clobazam tablets should be discontinued at the first sign of rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered *[see Contraindications (4)].*

5.6 Physical and Psychological Dependence

Patients with a history of substance abuse should be under careful surveillance when receiving clobazam tablets or other psychotropic agents because of the predisposition of such patients to habituation and dependence *[see Drug Abuse and Dependence (9)]*.

5.7 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including clobazam tablets, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted relative risk 1.8, 95% confidence interval [CI]: 1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing clobazam tablets or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include the following:

- Risks from Concomitant Use with Opioids *[see Warnings and Precautions (5.1)]*
- Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants *[see Warnings and Precautions (5.2)]*
- Somnolence or Sedation *[see Warnings and Precautions (5.3)]*
- Withdrawal Symptoms *[see Warnings and Precautions (5.4)]*
- Serious Dermatological Reactions *[see Contraindications (4), Warnings and Precautions (5.5)]*
- Physical and Psychological Dependence *[see Warnings and Precautions (5.6)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During its development for the adjunctive treatment of seizures associated with LGS, clobazam tablets 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) *[see Clinical Studies (14)]*. Only Study 1 included a placebo group, allowing comparison of adverse reaction rates on clobazam tablets at several doses to placebo.

Adverse Reactions Leading to Discontinuation in an LGS Placebo Controlled Clinical Trial (Study 1)

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

Most Common Adverse Reactions in an LGS Placebo Controlled Clinical Trial (Study 1)

Table 3 lists the adverse reactions that occurred in ≥5% of clobazam tablets-treated patients (at any dose), and at a rate greater than placebo-treated patients, in the randomized, double-blind, placebo-controlled, parallel group clinical study of adjunctive AED therapy for 15 weeks (Study 1).

Table 3. Adverse Reactions Reported for ≥5% of Patients and More Frequently than Placebo in Any Treatment Group

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

[a]Maximum daily dose of 5 mg for ≤30 kg body weight; 10 mg for >30 kg body weight
[b]Maximum daily dose of 10 mg for ≤30 kg body weight; 20 mg for >30 kg body weight
[c]Maximum daily dose of 20 mg for ≤30 kg body weight; 40 mg for >30 kg body weight

6.2 Postmarketing Experience

These reactions are reported voluntarily from a population of uncertain size; therefore, it is not possible to estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions are categorized by system organ class.

Blood Disorders: Anemia, eosinophilia, leukopenia, thrombocytopenia

Eye Disorders: Diplopia, vision blurred

Gastrointestinal Disorders: Abdominal distention

General Disorders and Administration Site Conditions: Hypothermia

Investigations: Hepatic enzyme increased

Musculoskeletal: Muscle spasms

Psychiatric Disorders: Agitation, anxiety, apathy, confusional state, depression, delirium, delusion, hallucination

Renal and Urinary Disorders: Urinary retention

Respiratory Disorders: Aspiration, respiratory depression

Skin and Subcutaneous Tissue Disorders: Rash, urticaria, angioedema, and facial and lip edema

7 DRUG INTERACTIONS

7.1 Opioids

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation *[see Warnings and Precautions (5.1)]*.

7.2 CNS Depressants and Alcohol

Concomitant use of clobazam tablets with other CNS depressants may increase the risk of sedation and somnolence *[see Warnings and Precautions (5.2)]*.

Alcohol, as a CNS depressant, will interact with clobazam in a similar way and also increases clobazam's maximum plasma exposure by approximately 50%. Therefore, caution patients or their caregivers against simultaneous use with other CNS depressant drugs or alcohol, and caution that the effects of other CNS depressant drugs or alcohol may be potentiated *[see Warnings and Precautions (5.2)]*.

7.3 Effect of Clobazam on Other Drugs

Hormonal Contraceptives

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 *[see Clinical Pharmacology (12.3), Patient Counseling Information (17)]*.

Drugs Metabolized by CYP2D6

Clobazam inhibits CYP2D6. Dose adjustment of drugs metabolized by CYP2D6 may be necessary *[see Clinical Pharmacology (12.3)]*.

7.4 Effect of Other Drugs on Clobazam

Strong and moderate inhibitors of CYP2C19

Strong and moderate inhibitors of CYP2C19 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 co-administered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole) *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AEDs, such as clobazam, during pregnancy. Physicians are advised to recommend that pregnant patients taking clobazam enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.

Risk Summary

There are no adequate and well-controlled studies of clobazam in pregnant women. Available data suggest that the class of benzodiazepines is not associated with marked increases in risk for congenital anomalies. Although some early epidemiological studies suggested a relationship between benzodiazepine drug use in pregnancy and congenital anomalies such as cleft lip and or palate, these studies had considerable limitations. More recently completed studies of benzodiazepine use in pregnancy have not consistently documented elevated risks for specific congenital anomalies. There is insufficient evidence to assess the effect of benzodiazepine pregnancy exposure on neurodevelopment.

There are clinical considerations regarding exposure to benzodiazepines during the second and third trimester of pregnancy or immediately prior to or during childbirth. These risks include decreased fetal movement and/or fetal heart rate variability, "floppy infant syndrome," dependence, and withdrawal *[see Clinical Considerations and Human Data]*.

Administration of clobazam to pregnant rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation resulted in developmental toxicity, including increased incidences of fetal malformations and mortality, at plasma exposures for clobazam and its major active metabolite, N-desmethylclobazam, below those expected at therapeutic doses in patients *[see Animal Data]*. Data for other benzodiazepines suggest the possibility of long-term effects on neurobehavioral and immunological function in animals following prenatal exposure to benzodiazepines at clinically relevant doses. Clobazam should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Advise a pregnant woman and women of childbearing age of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Clinical manifestations of withdrawal or neonatal abstinence syndrome may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhea, and vomiting. These complications can appear shortly after delivery to 3 weeks after birth and persist from hours to several months depending on the degree of dependence and the pharmacokinetic profile of the benzodiazepine. Symptoms may be mild and transient or severe. Standard management for neonatal withdrawal syndrome has not yet been defined. Observe newborns who are exposed to clobazam *in utero* during the later stages of pregnancy for symptoms of withdrawal and manage accordingly.

Labor and Delivery

Administration of benzodiazepines immediately prior to or during childbirth can result in a floppy infant syndrome, which is characterized by lethargy, hypothermia, hypotonia, respiratory depression, and difficulty feeding. Floppy infant syndrome occurs mainly within the first hours after birth and may last up to 14 days. Observe exposed newborns for these symptoms and manage accordingly.

Data

Human Data

Congenital Anomalies

Although there are no adequate and well controlled studies of clobazam in pregnant women, there is information about benzodiazepines as a class. Dolovich et al. published a meta-analysis of 23 studies that examined the effects of benzodiazepine exposure during the first trimester of pregnancy. Eleven of the 23 studies included in the meta-analysis considered the use of chlordiazepoxide and diazepam and not other benzodiazepines. The authors considered case-control and cohort studies separately. The data from the cohort studies did not suggest an increased risk for major malformations (OR 0.90; 95% CI 0.61 to 1.35) or for oral cleft (OR 1.19; 95% CI 0.34 to 4.15). The data from the case-control studies suggested an association between benzodiazepines and major malformations (OR 3.01, 95% CI 1.32 to 6.84) and oral cleft (OR 1.79; 95% CI 1.13 to 2.82). The limitations of this meta-analysis included the small number of reports included in the analysis, and that most cases for analyses of both oral cleft and major malformations came from only three studies. A follow up to that meta-analysis included 3 new cohort studies that examined risk for major malformations and one study that considered cardiac malformations. The authors found no new studies with an outcome of oral clefts. After the addition of the new studies, the odds ratio for major malformations with first trimester exposure to benzodiazepines was 1.07 (95% CI 0.91 to 1.25).

Neonatal Withdrawal and Floppy Infant Syndrome

Neonatal withdrawal syndrome and symptoms suggestive of floppy infant syndrome associated with administration of clobazam during the later stages of pregnancy and peripartum period have been reported in the postmarketing experience. Findings in published scientific literature suggest that the major neonatal side effects of benzodiazepines include sedation and dependence with withdrawal signs. Data from observational studies suggest that fetal exposure to benzodiazepines is associated with the neonatal adverse events of hypotonia, respiratory problems, hypoventilation, low Apgar score, and neonatal withdrawal syndrome.

Animal Data

In a study in which clobazam (0, 150, 450, or 750 mg/kg/day) was orally administered to pregnant rats throughout the period of organogenesis, embryofetal mortality and incidences of fetal skeletal variations were increased at all doses. The low-effect dose for embryofetal developmental toxicity in rats (150 mg/kg/day) was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, lower than those in humans at the maximum recommended human dose (MRHD) of 40 mg/day.

Oral administration of clobazam (0, 10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality at the high dose. Incidences of fetal variations were increased at all doses. The highest dose tested was associated with maternal toxicity (ataxia and decreased activity). The low-effect dose for embryofetal developmental toxicity in rabbits (10 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD.

Oral administration of clobazam (0, 50, 350, or 750 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased embryofetal mortality at the high dose, decreased pup survival at the mid and high doses and alterations in offspring behavior (locomotor activity) at all doses. The low-effect dose for adverse effects on pre- and postnatal development in rats (50 mg/kg/day) was associated with plasma exposures for clobazam and N-desmethylclobazam lower than those in humans at the MRHD.

8.2 Lactation

Risk Summary

Clobazam is excreted in human milk. Postmarketing experience suggests that breastfed infants of mothers taking benzodiazepines, such as clobazam, may have effects of lethargy, somnolence and poor sucking. The effect of clobazam on milk production is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for clobazam and any potential adverse effects on the breastfed infant from clobazam or from the underlying maternal condition. If exposing a breastfed infant to clobazam, observe for any potential adverse effects.

Clinical Considerations

Monitoring for Adverse Reactions

Adverse reactions such as somnolence and difficulty feeding have been reported in infants during breastfeeding in postmarketing experience with clobazam. Monitor breastfed infants for possible sedation and poor sucking.

Data

Scientific literature on clobazam use during lactation is limited. After short-term administration, clobazam and N-desmethylclobazam are transferred into breast milk.

8.3 Females and Males of Reproductive Potential

Administration of clobazam to rats prior to and during mating and early gestation resulted in adverse effects on fertility and early embryonic development at plasma exposures for clobazam and its major active metabolite, N-desmethylclobazam, below those in humans at the MRHD *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness in patients less than 2 years of age have not been established.

In a study in which clobazam (0, 4, 36 or 120 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 14 to 48), adverse effects on growth (decreased bone density and bone length) and behavior (altered motor activity and auditory startle response; learning deficit) were observed at the high dose. The effect on bone density, but not on behavior, was reversible when drug was discontinued. The no-effect level for juvenile toxicity (36 mg/kg/day) was associated with plasma exposures (AUC) to clobazam and its major active metabolite, N-desmethylclobazam, less than those expected at therapeutic doses in pediatric patients.

8.5 Geriatric Use

Clinical studies of clobazam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, elderly subjects appear to eliminate clobazam more slowly than younger subjects based on population pharmacokinetic analysis. For these reasons, the initial dose in elderly patients should be 5 mg/day. Patients should be titrated initially to 10 mg to 20 mg/day. Patients may be titrated further to a maximum daily dose of 40 mg if tolerated *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.6 CYP2C19 Poor Metabolizers

Concentrations of clobazam's active metabolite, N-desmethylclobazam, are higher in CYP2C19 poor metabolizers than in extensive metabolizers. For this reason, dosage modification is recommended *[see Dosage and Administration (2.5), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

The pharmacokinetics of clobazam were evaluated in patients with mild and moderate renal impairment. There were no significant differences in systemic exposure (AUC and C_{max}) between patients with mild or moderate renal impairment and healthy subjects. No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with clobazam in patients with severe renal impairment or ESRD. It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment

Clobazam is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam tablets. For this reason, dosage adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh score 5 to 9). There is inadequate information about metabolism of clobazam in patients with severe hepatic impairment *[see Dosage and Administration (2.7), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Clobazam tablet contains clobazam which is a Schedule IV controlled substance.

9.2 Abuse

Clobazam can be abused in a similar manner as other benzodiazepines, such as diazepam.

The pharmacological profile of clobazam is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on $GABA_A$ receptors, which leads to sedation and somnolence.

The World Health Organization epidemiology database contains reports of drug abuse, misuse, and overdoses associated with clobazam.

Drug abuse is the intentional non-therapeutic use of a drug, repeatedly or even sporadically, for its rewarding psychological or physiological effects.

9.3 Dependence

Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist. In clinical trials, cases of dependency were reported following abrupt discontinuation of clobazam tablets.

The risk of dependence is present even with use of clobazam tablets at the recommended dose range over periods of only a few weeks. The risk of dependence increases with increasing dose and duration of treatment. The risk of dependence is increased in patients with a history of alcohol or drug abuse.

Withdrawal

Abrupt discontinuation of clobazam tablets causes withdrawal symptoms. As with other benzodiazepines, clobazam should be withdrawn gradually *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.

In clobazam clinical pharmacology trials in healthy volunteers, the most common withdrawal symptoms after abrupt discontinuation were headache, tremor, insomnia, anxiety, irritability, drug withdrawal syndrome, palpitations, and diarrhea *[see Warnings and Precautions (5.4)]*.

Other withdrawal reactions to clobazam reported in the literature include restlessness, panic attacks, profuse sweating, difficulty in concentrating, nausea and dry retching, weight loss, blurred vision, photophobia, and muscle pain and stiffness. In general, benzodiazepine withdrawal may cause seizures, psychosis, and hallucinations *[see Warnings and Precautions (5.4)]*.

10 OVERDOSAGE

10.1 Signs and Symptoms of Overdosage

Overdose and intoxication with benzodiazepines, including clobazam, may lead to CNS depression, associated with drowsiness, confusion and lethargy, possibly progressing to ataxia, respiratory depression, hypotension, and, rarely, coma or death. The risk of a fatal outcome is increased in cases of combined poisoning with other CNS depressants, including opioids and alcohol.

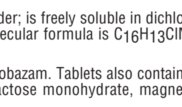
10.2 Management of Overdosage

The management of clobazam overdose may include gastric lavage and/or administration of activated charcoal, intravenous fluid replenishment, early control of airway and general supportive measures, in addition to monitoring level of consciousness and vital signs. 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 of flumazenil (a benzodiazepine antagonist) in clobazam overdose has not been assessed. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions. Its use in patients with epilepsy is typically not recommended.

11 DESCRIPTION

Table 4. Description

Proprietary Name:	Not Applicable
Established Name:	Clobazam Tablets
Dosage Forms:	Tablet
Route of Administration:	Oral
Established Pharmacologic Class of Drug:	Benzodiazepine
Chemical Name:	7-Chloro-1-methyl-5-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione
Structural Formula:	

Clobazam is a white or almost white, crystalline powder; is freely soluble in dichloromethane. The melting range of clobazam is from 180ºC to 182ºC. The molecular formula is $C_{16}H_{13}ClN_2O_2$ and the molecular weight is 300.74.

Each clobazam tablet contains 10 mg or 20 mg of clobazam. Tablets also contain as inactive ingredients: colloidal silicon dioxide, granulated corn starch, lactose monohydrate, magnesium stearate and talc.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 binding at the benzodiazepine site of the $GABA_A$ receptor.

12.2 Pharmacodynamics

Effects on Electrocardiogram

The effect of clobazam tablets 20 mg and 80 mg administered twice daily on QTc interval was evaluated in a randomized, evaluator-blinded, placebo-, and active-controlled (moxifloxacin 400 mg) parallel thorough QT study in 280 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on the Fridericia correction method was below 10 ms, the threshold for regulatory concern. Thus, at a dose two times the maximum recommended dose, clobazam did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10 mg to 80 mg following single- or multiple-dose administration of clobazam. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5 mg to 160 mg/day. Clobazam is converted to N-desmethylclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives ($t_{½}$) of clobazam and N-desmethylclobazam were 36 to 42 hours and 71 to 82 hours, respectively.

Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (T_{max}) of clobazam tablets under fasted conditions ranged from 0.5 to 4 hours after single- or multiple-dose administrations. The relative bioavailability of clobazam tablets compared to an oral solution is approximately 100%. After single dose administration of the oral suspension under fasted conditions, the T_{max} ranged from 0.5 to 2 hours. Based on exposure (C_{max} and AUC) of clobazam, clobazam tablets and suspension were shown to have similar bioavailability under fasted conditions. The administration of clobazam tablets with food or when crushed in applesauce does not affect absorption.

Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. 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 to 90% and 70%, respectively.

Metabolism and Excretion

Clobazam is extensively metabolized in the liver, with approximately 2% of the dose recovered in urine and 1% in feces as unchanged drug. The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethylclobazam, an active metabolite, is the major circulating metabolite in humans, and at therapeutic doses, plasma concentrations are 3 to 5 times higher than those of the parent compound. Based on animal and *in vitro* receptor binding data, estimates of the relative potency of N-desmethylclobazam compared to parent compound range from 1/5 to equal potency. N-desmethylclobazam is extensively metabolized, mainly by CYP2C19. N-desmethylclobazam and its metabolites comprise ~94% of the total drug-related components in urine. Following a single oral dose of radiolabeled drug, approximately 11% of the dose was excreted in the feces and approximately 82% was excreted in the urine.

The polymorphic CYP2C19 is the major contributor to the metabolism of the pharmacologically active N-desmethylclobazam *[see Clinical Pharmacology (12.5)]*. In CYP2C19 poor metabolizers, levels of N-desmethylclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

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Pharma code :

Pharmacokinetics in Specific Populations

Age

Population pharmacokinetic analyses showed that the clearance of clobazam is lower in elderly subjects compared to other age groups (ages 2 to 64). Dosing should be adjusted in the elderly *[see Dosage and Administration (2.4)]*.

Sex

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.

Renal Impairment

The effect of renal impairment on the pharmacokinetics of clobazam was evaluated in patients with mild (creatinine clearance [CL_{CR}] >50 to 80 mL/min; N=6) and moderate (CL_{CR}=30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of clobazam tablets 20 mg/day. There were insignificant changes in C_{max} (3 to 24%) and AUC (<13%) for clobazam or N-desmethylclobazam in patients with mild or moderate renal impairment compared to patients with normal renal function. Patients with severe renal impairment or ESRD were not included in this study.

Hepatic Impairment

There are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of clobazam. In a small study, the pharmacokinetics of a 20 mg single oral dose of clobazam in 9 patients with liver impairment were compared to healthy controls (N=6). The C_{max} and the mean plasma clearance of clobazam, as well as the C_{max} of N-desmethylclobazam, showed no significant change compared to the healthy controls. The AUC values of N-desmethylclobazam in these patients were not available. Adjust dosage in patients with hepatic impairment *[see Dosage and Administration (2.7)]*.

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 in a concentration-dependent manner. Clobazam and N-desmethylclobazam also increased UGT1A1 mRNA but at concentrations much higher than therapeutic 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.

In vivo studies:

Potential for Clobazam to Affect Other Drugs

The effect of repeated 40 mg once-daily doses of clobazam on the pharmacokinetic profiles of single-dose dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), and tolbutamide (CYP2C9 substrate), was studied when these probe substrates were given as a drug cocktail (N=18).

Clobazam increased AUC and C_{max} of dextromethorphan by 90% and 59%, respectively, reflecting its inhibition of CYP2D6 *in vivo*. Drugs metabolized by CYP2D6 may require dose adjustment when used with clobazam.

Clobazam decreased the AUC and C_{max} of midazolam by 27% and 24%, respectively, and increased the AUC and C_{max} of the metabolite 1-hydroxymidazolam by 4-fold and 2-fold, respectively. This level of induction does not call for dosage adjustment of drugs that are primarily metabolized by CYP3A4 when used concomitantly with clobazam. Some hormonal contraceptives are metabolized by CYP3A4 and their effectiveness may be diminished when given with clobazam *[see Drug Interactions (7.3)]*. Repeated clobazam doses had no effect on caffeine and tolbutamide.

A population pharmacokinetic analysis indicated clobazam did not affect the exposure of valproic acid (a CYP2C9/2C19 substrate) or lamotrigine (a UGT substrate).

Potential for Other Drugs to Affect Clobazam

Co-administration of ketoconazole (a strong CYP3A4 inhibitor) 400 mg once-daily for 5 days increased clobazam AUC by 54%, with an insignificant effect on clobazam C_{max}. There was no significant change in AUC and C_{max} of N-desmethylclobazam (N=18).

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 *[see Clinical Pharmacology (12.5)]*. Dosage adjustment of clobazam may be necessary when co-administered with strong or moderate CYP2C19 inhibitors *[see Drug Interactions (7.4)]*.

The effects of concomitant antiepileptic drugs that are CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C19 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C19 inhibitors (felbamate and oxcarbazepine) were evaluated using data from clinical trials. Results of population pharmacokinetic analysis show that these concomitant antiepileptic drugs did not significantly alter the pharmacokinetics of clobazam or N-desmethylclobazam at steady-state.

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 tablets *[see Warnings and Precautions (5.2), Drug Interactions (7.2)]*.

12.5 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 to 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 (2.5)]*.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In mice, oral administration of clobazam (0, 6, 12, or 24 mg/kg/day) for 2 years did not result in an increase in tumors. The highest dose tested was approximately 3 times the maximum recommended human dose (MRHD) of 40 mg/day, based on body surface area (mg/m^2).

In rats, oral administration of clobazam for 2 years resulted in increases in tumors of the thyroid gland (follicular cell adenoma and carcinoma) and liver (hepatocellular adenoma) at the mid and high doses. The low dose, not associated with an increase in tumors, was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, less than that in humans at the MRHD.

Mutagenesis

Clobazam and the major active metabolite, N-desmethylclobazam, were negative for genotoxicity, based on data from a battery of *in vitro* (bacteria reverse mutation, mammalian clastogenicity) and *in vivo* (mouse micronucleus) assays.

Impairment of Fertility

In a fertility study in which clobazam (50, 350, or 750 mg/kg/day, corresponding to 12, 84 and 181 times the oral Maximum Recommended Human Dose, MRHD, of 40 mg/day based on mg/m^2 body surface) was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6, increases in abnormal sperm and pre-implantation loss were observed at the highest dose tested. The no-effect level for fertility and early embryonic development in rats was associated with plasma exposures (AUC) for clobazam and its major active metabolite, N-desmethylclobazam, less than those in humans at the maximum recommended human dose of 40 mg/day.

14 CLINICAL STUDIES

The effectiveness of clobazam for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome was established in two multicenter controlled studies (Study 1 and Study 2). Both studies were similar in terms of disease characteristics and concomitant AED treatments. The most common concomitant AED treatments at baseline included: valproate, lamotrigine, levetiracetam, and topiramate.

Study 1

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. Patients age 2 to 54 years with a current or prior diagnosis of LGS were stratified into 2 weight groups (12.5 kg to ≤30 kg or >30 kg) and then randomized to placebo or one of three target maintenance doses of clobazam according to Table 5.

Table 5. Study 1 Total Daily Dose

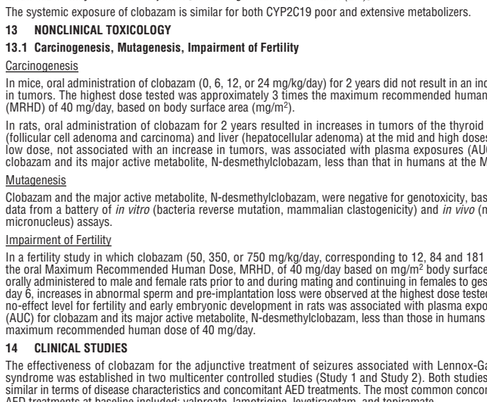
	≤30 kg Body Weight	>30 kg Body Weight
Low Dose	5 mg daily	10 mg daily
Medium Dose	10 mg daily	20 mg daily
High Dose	20 mg daily	40 mg daily

Doses above 5 mg/day were administered in two divided doses.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to 12-week maintenance period.

The pre-dosing baseline mean weekly drop seizure frequency was 98, 100, 61, and 105 for the placebo, low-, medium-, and high-dose groups, respectively. Figure 1 presents the mean percent reduction in weekly drop seizures from this baseline. All dose groups of clobazam were statistically superior ($p \leq 0.05$) to the placebo group. This effect appeared to be dose dependent.

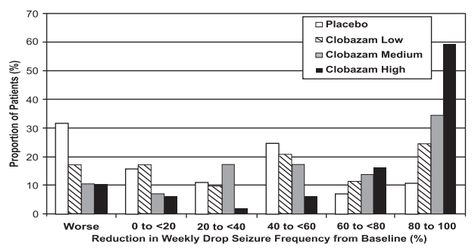
Figure 1. Mean Percent Reduction from Baseline in Weekly Drop Seizure Frequency (Study 1)



* p < 0.05, **p < 0.01

Figure 2 shows changes from baseline in weekly drop seizure frequency by category for patients treated with clobazam and placebo in Study 1. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

Figure 2. Drop Seizure Response by Category for Clobazam and Placebo (Study 1)



There was no evidence that tolerance to the therapeutic effect of clobazam developed during the 3-month maintenance period.

Study 2

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. Patientsage 2 to 25 years with a current or prior diagnosis of LGS were stratified by weight, then randomized to either a low or high dose of clobazam, and then entered a 3-week titration period.

The primary efficacy measure was the percent reduction in the weekly frequency of drop seizures (atonic, tonic, or myoclonic), also known as drop attacks, from the 4-week baseline period to the 4-week maintenance period.

A statistically significantly greater reduction in seizure frequency was observed in the high-dose group compared to the low-dose group (median percent reduction of 93% vs 29%; p<0.05).

16 HOW SUPPLIED/STORAGE AND HANDLING

Clobazam tablets, 10 mg are white to off white, oval tablets debossed 'C' and '9' along with functional score on one side and 'H' on the other side. They are supplies as follows:

Bottles of 100 tablets	NDC 31722-639-01
Carton of 100 (10 x10) unit-dose tablets	NDC 31722-639-31

Clobazam tablets, 20 mg are white to off white, oval tablets debossed 'C' and '13' along with functional score on one side and 'H' on the other side.

Bottles of 100 tablets	NDC 31722-640-01
Carton of 100 (10x10) unit-dose tablets	NDC 31722-640-31

Store tablets at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risks from Concomitant Use with Opioids

Inform patients and caregivers that potentially fatal additive effects may occur if clobazam tablet is used with opioids and not to use such drugs concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Somnolence or Sedation

Advise patients or caregivers to check with their healthcare provider before clobazam tablet is taken with other CNS depressants such as other benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or alcohol *[see Warnings and Precautions (5.2, 5.3)]*.

If applicable, caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain that clobazam tablets does not affect them adversely (e.g., impair judgment, thinking or motor skills).

Increasing or Decreasing the Clobazam Dose

Inform patients or caregivers to consult their healthcare provider before increasing the clobazam tablets dose or abruptly discontinuing clobazam tablets. Advise patients or caregivers that abrupt withdrawal of AEDs may increase their risk of seizure *[see Dosage and Administration (2.2), Warnings and Precautions (5.4)]*.

Hypersensitivity

Inform patients or caregivers that clobazam tablet is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients *[see Warnings and Precautions (5.5)]*.

Interactions with Hormonal Contraceptives

Counsel women to also use non-hormonal methods of contraception when clobazam tablet is used with hormonal contraceptives and to continue these alternative methods for 28 days after discontinuing clobazam tablets to ensure contraceptive reliability *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.

Serious Dermatological Reactions

Advise patients or caregivers that serious skin reactions have been reported in patients taking clobazam tablets. Serious skin reactions, including SJS/TEN, may need to be treated in a hospital and may be life-threatening. If a skin reaction occurs while taking clobazam tablets, patients or caregivers should consult with healthcare providers immediately *[see Warnings and Precautions (5.5)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that AEDs, including clobazam tablets, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Patients should report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.7)]*.

Pregnancy

Advise pregnant women and women of childbearing potential that the use of clobazam tablets during pregnancy can cause fetal harm which may occur early in pregnancy before many women know they are pregnant. Instruct patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy. When appropriate, prescribers should counsel pregnant women and women of childbearing potential about alternative therapeutic options.

Advise patients that there is a pregnancy exposure registry that collects information about the safety of antiepileptic drugs during pregnancy *[see Use in Specific Populations (8.1)]*.

Nursing

Counsel patients that clobazam is excreted in breast milk. Instruct patients to notify their physician if they are breast feeding or intend to breast feed during therapy and counsel nursing mothers to observe their infants for poor sucking and somnolence *[see Use in Specific Populations (8.2)]*.

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Revised: September 2018

2050284

MEDICATION GUIDE
Clobazam
(KLOE ba zam)
Tablets CIV

What is the most important information I should know about clobazam tablets?

- **Do not stop taking clobazam tablets without first talking to your healthcare provider.** Stopping clobazam tablets suddenly can cause serious side effects.
- **Clobazam tablet is a benzodiazepine medicine. Benzodiazepines can cause severe drowsiness, breathing problems (respiratory depression), coma, and death when taken with opioid medicines.**
- **Clobazam tablets can make you sleepy or dizzy and can slow your thinking and motor skills. This may get better over time.**
  - Do not drive, operate heavy machinery, or do other dangerous activities until you know how clobazam tablets affect you.
  - Clobazam tablets may cause problems with your coordination, especially when you are walking or picking things up.
- **Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking clobazam tablets until you talk to your healthcare provider.** When taken with alcohol or drugs that cause sleepiness or dizziness, clobazam tablets may make your sleepiness or dizziness much worse.
- **Clobazam tablets can cause withdrawal symptoms.**
  - Do not stop taking clobazam tablets all of a sudden without first talking to a healthcare provider. Stopping clobazam tablets suddenly can cause seizures that will not stop (status epilepticus), hearing or seeing things that are not there (hallucinations), shaking, nervousness, and stomach and muscle cramps.
  - Talk to your healthcare provider about slowly stopping clobazam tablets to avoid withdrawal symptoms.
- **Clobazam tablets can be abused and cause dependence.**
  - Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.
- **Clobazam tablet is a federal controlled substance (CIV) because it can be abused or lead to dependence**. Keep clobazam tablets in a safe place to prevent misuse and abuse. Selling or giving away clobazam tablets may harm others, and is against the law. Tell your healthcare provider if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.
- **Serious skin reactions have been seen when clobazam tablets are taken with other medicines and may require stopping its use.** Do not stop taking clobazam tablets without first talking to your healthcare provider.
  - A serious skin reaction can happen at any time during your treatment with clobazam tablets, but is more likely to happen within the first 8 weeks of treatment. These skin reactions may need to be treated right away.
  - Call your healthcare provider immediately if you have skin blisters, rash, sores in the mouth, hives or any other allergic reaction.
- **Like other antiepileptic drugs, clobazam tablets may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- new or worse anxiety
- trouble sleeping (insomnia)
- acting on dangerous impulses
- attempts to commit suicide
- feeling agitated or restless
- new or worse irritability
- an extreme increase in activity and talking (mania)
- new or worse depression
- panic attacks
- acting aggressive, being angry, or violent
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What are clobazam tablets?

Clobazam tablets are a prescription medicine used along with other medicines to treat seizures associated with Lennox-Gastaut syndrome in people 2 years of age or older.

It is not known if clobazam tablets are safe and effective in children less than 2 years old.

Do not take clobazam tablets if you:

- are allergic to clobazam or any of the ingredients in clobazam tablets. See the end of this Medication Guide for a complete list of ingredients in clobazam tablets.

Before you take clobazam tablets, tell your healthcare provider about all your medical conditions, including if you:

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- use birth control medicine. Clobazam tablets may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. **Clobazam tablets may harm your unborn baby.**
  - Tell your healthcare provider right away if you become pregnant while taking clobazam tablets. You and your healthcare provider will decide if you should take clobazam tablets while you are pregnant.
  - Babies born to mothers receiving benzodiazepine medications (including clobazam tablets) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, dangerously low body temperature, and withdrawal symptoms.
- If you become pregnant while taking clobazam tablets, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. For more information about the registry go to http://www.aedpregnancyregistry.org. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- Clobazam can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take clobazam tablets. You and your healthcare provider should decide if you will take clobazam tablets or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking clobazam tablets with certain other medicines can cause side effects or affect how well clobazam tablets or the other medicines work. Do not start or stop other medicines without talking to your healthcare provider.

How should I take clobazam tablets?

- Take clobazam tablets exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much clobazam to take and when to take it.
- Clobazam tablets can be taken whole, broken in half along the score, or crushed and mixed in applesauce.
- Clobazam tablets can be taken with or without food.
- Your healthcare provider may change your dose if needed. Do not change your dose of clobazam tablets without talking to your healthcare provider.
- Do not stop taking clobazam tablets without first talking to your healthcare provider.
- Stopping clobazam tablets suddenly can cause serious problems.
- If you take too much clobazam, call your healthcare provider or go to the nearest hospital emergency room right away.

What should I avoid while taking clobazam tablets?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how clobazam tablets affect you.
- Do not drink alcohol or take other medicines that may make you sleepy or dizzy while taking clobazam tablets until you talk to your healthcare provider. When taken with alcohol or medicines that cause sleepiness or dizziness, clobazam tablets may make your sleepiness or dizziness much worse.

What are the possible side effects of clobazam tablets?

Clobazam tablets may cause serious side effects, including: See "What is the most important information I should know about clobazam tablets?"

The most common side effects of clobazam tablets include:

- sleepiness
- cough
- acting aggressive, being angry, or violent
- tiredness
- drooling
- pain with urination
- difficulty sleeping
- problems with breathing
- constipation
- fever
- slurred speech

These are not all the possible side effects of clobazam tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store clobazam tablets?

- Store clobazam tablets between 68°F to 77°F (20°C to 25°C).
- Keep clobazam tablets in a dry place.

Keep clobazam tablets and all medicines out of the reach of children.

General information about the safe and effective use of clobazam tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use clobazam tablets for a condition for which it was not prescribed. Do not give clobazam tablets to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about clobazam tablets that is written for health professionals.

For more information, call 1-866-495-1995.

What are the ingredients in clobazam tablets?

Active ingredient: clobazam

Inactive ingredients: colloidal silicon dioxide, granulated corn starch, lactose monohydrate, magnesium stearate and talc.

Medication Guide available at
http://camberpharma.com/medication-guides

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 09/2018