

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

CLOGABA 10 MG TABLET

2. Qualitative and quantitative composition

Each uncoated tablet contains Clobazam 10 mg

Excipients with potential clinical effect:

Each uncoated tablet contains Lactose.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Uncoated Tablet.

White to off white, oval shaped uncoated tablets with functional score on one side and “C” and “M” debossed on the other side.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

4.2.1 Dosing Information

A daily dose of Clobazam 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 to 20 mg in ≤30 kg weight group) has been shown to be effective, although effectiveness increases with increasing dose. 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

4.2.2 Gradual Withdrawal

As with all antiepileptic drugs and benzodiazepines, withdraw Clobazam gradually. Taper by decreasing the total daily dose by 5-10 mg/day on a weekly basis until discontinued [see Warnings and Precautions (4.4)].

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.

4.2.4 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.

4.2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers

In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 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.

4.2.6 Patients with Renal Impairment

No dose adjustment is required for patients with mild and moderate renal impairment. There is no experience with Clobazam in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or its active metabolite, N-desmethyloclobazam, is dialyzable.

4.2.7 Dosage Adjustments in Patients with Hepatic Impairment

Clobazam is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of Clobazam. For this reason, proceed slowly with dosing escalations. For patients with mild to moderate hepatic impairment (Child-Pugh score 5-9), 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 in patients with severe hepatic impairment.

4.3 Contraindications

Clobazam 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 (4.4)].

4.4 Special warnings and precautions for use

4.4.1 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 (4.5)].

4.4.2 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 (4.5)].

4.4.3 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.

4.4.4 Withdrawal Symptoms

Abrupt discontinuation of Clobazam should be avoided. Clobazam should be tapered by decreasing the dose every week by 5-10 mg/day until discontinuation [see Posology and Administration (4.2)]. Withdrawal symptoms occurred following abrupt discontinuation of Clobazam; the risk of withdrawal symptoms is greater with higher doses.

As with all antiepileptic drugs, Clobazam 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.

4.4.5 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 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 (4.3)]

4.4.6 Physical and Psychological Dependence

Patients with a history of substance abuse should be under careful surveillance when receiving Clobazam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

4.4.7 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Clobazam, 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% cClobazamdenance 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 (5-100 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 1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	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 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.

4.5 Drug Interactions

4.5.1 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 GABAA 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 (4.4)].

4.5.2 CNS Depressants and Alcohol

Concomitant use of Clobazam with other CNS depressants may increase the risk of sedation and somnolence [see Warnings and Precautions (4.4)].

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 (4.4)].

4.5.3 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.

Drugs Metabolized by CYP2D6

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

4.5.4 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-desmethyclobazam, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy:

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.

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-desmethyloclobazam, 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 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Breast-feeding:

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.

Fertility:

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-desmethyloclobazam, below those in humans at the MRHD.

4.7 Undesirable effects

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 (4.4)]
- Potentiation of Sedation from Concomitant Use with Central Nervous System Depressants [see Warnings and Precautions (4.4)]
- Somnolence or Sedation [see Warnings and Precautions (4.4)]
- Withdrawal Symptoms [see Warnings and Precautions (4.4)]
- Serious Dermatological Reactions [see Contraindications (4), Warnings and Precautions (4.4)]
- Physical and Psychological Dependence [see Warnings and Precautions (4.4)]
- Suicidal Behavior and Ideation [see Warnings and Precautions (4.4)]

4.7.1 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 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.

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

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

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

Table 3 lists the adverse reactions that occurred in $\geq 5\%$ of Clobazam-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 $\geq 5\%$ 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	15	17	27	32	26
or Sedation					
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

4.8 Overdose

4.8.1 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.

4.8.2 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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC Code: N05BA09 (Nervous System, Psycholeptics, Anxiolytics, Benzodiazepine derivatives, Clobazam)

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 receptor.

Effects on Electrocardiogram

The effect of Clobazam 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% cClobazam dence 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.

5.2 Pharmacokinetic properties

The peak plasma levels (C_{max}) and the area under the curve (AUC) of clobazam are dose-proportional over the dose range of 10-80 mg following single- or multiple-dose administration of Clobazam. Based on a population pharmacokinetic analysis, the pharmacokinetics of clobazam are linear from 5-160 mg/day. Clobazam is converted to N-desmethyloclobazam which has about 1/5 the activity of clobazam. The estimated mean elimination half-lives (t_{1/2}) of clobazam and N-desmethyloclobazam were 36-42 hours and 71-82 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. Although not studied, the oral bioavailability of the oral suspension is unlikely to be affected under fed conditions.

Distribution

Clobazam is lipophilic and distributes rapidly throughout the body. The apparent volume of distribution at steady state was approximately 100 L. The invitro plasma protein binding of clobazam and N-desmethyloclobazam is approximately 80-90% 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-desmethyloclobazam, an active metabolite, is the major circulating metabolite in humans, and at therapeutic doses, plasma concentrations are 3-5 times higher than those of the parent compound. Based on animal and in vitro receptor binding data, estimates of the relative potency of N-desmethyloclobazam compared to parent compound range from 1/5 to equal potency. N-desmethyloclobazam is extensively metabolized, mainly by CYP2C19. N-desmethyloclobazam 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-desmethyloclobazam. In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam were 5-fold higher in plasma and 2- to 3-fold higher in the urine than in CYP2C19 extensive metabolizers.

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 (4.2)].

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 [CLCR] >50 to 80 mL/min; N=6) and moderate (CLCR=30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of Clobazam 20 mg/day. There were insignificant changes in C_{max} (3-24%) and AUC (≤13%) for clobazam or N-desmethyclobazam 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-desmethyclobazam, showed no significant change compared to the healthy controls. The AUC values of N-desmethyclobazam in these patients were not available. Adjust dosage in patients with hepatic impairment [see Dosage and Administration (4.2)].

Drug Interaction Studies

In vitro studies:

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

Clobazam and N-desmethyclobazam did not significantly increase CYP1A2 or CYP2C19 activities, but did induce CYP3A4 activity in a concentration-dependent manner. Clobazam and N-desmethyclobazam also increased UGT1A1 mRNA but at concentrations much higher than therapeutic levels. The potential for clobazam or N-desmethyclobazam to induce CYP2B6 and CYP2C8 has not been evaluated.

Clobazam and N-desmethyclobazam 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 (4.5)]. 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-desmethyloclobazam (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-desmethyloclobazam, the active metabolite of clobazam, based on extrapolation from pharmacogenomic data. Dosage adjustment of Clobazam may be necessary when co-administered with strong or moderate CYP2C19 inhibitors [see Drug Interactions (4.5)].

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 desmethyloclobazam 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 [see Warnings and Precautions (4.4), Drug Interactions (4.5)]

5.3 Preclinical safety data

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/m²). 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-desmethyclobazam, less than that in humans at the MRHD.

Mutagenesis

Clobazam and the major active metabolite, N-desmethyclobazam, 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/m² 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-desmethyclobazam, less than those in humans at the maximum recommended human dose of 40 mg/day.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate
Corn Starch
Hydroxypropyl Cellulose
Colloidal silicon dioxide
Talc
Magnesium stearate
Purified water.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

10 Tablets of Clobazam Tablets 10 mg are sealed with Clear PVC base foil on one side and plain Lidding foil on other side in the form of an Alu-PVC blister pack.

1 or 3 or 10 such blisters are further packed in printed carton along with instructions for use.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

MSN Laboratories Private Limited Formulation Division,
Unit-II, Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal), Rangareddy (District),
Telangana - 509 228, India.

8. Marketing authorization number(s)

H2025/CTD9309/20170

9. Date of first registration/ renewal of the registration

2025 May 22

10. Date of revision of the text

2025 May 22