**PRESCRIBING INFORMATION:** For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

# CLOBA MT 5/10

(CLOBAZAM MOUTH DISSOLVING TABLETS 5/10 mg)

**Composition**

**CLOBA MT 5**

Each uncoated tablet contains:
Clobazam IP 5 mg
Excipients: Q.S.

**CLOBA MT 10**

Each uncoated tablet contains:
Clobazam IP 10 mg
Excipients: Q.S.

**Description**

Clobazam is a 1,5-benzodiazepine with anticonvulsant properties. Chemically, clobazam is 7-chloro-1-methyl-5-phenyl-1H-1,5-benzodiazepine 2, 4 (3H, 5H)dione. The molecular formula is $C_{16}H_{13}O_2N_2Cl$ and molecular weight is 300.7.

**Clinical Pharmacology**

**Pharmacodynamics**

Pharmacologic studies in animals have shown that clobazam can suppress seizures induced by a variety of experimental procedures. With respect to electro-shock induced seizures in the mouse, clobazam is more effective than valproic acid but less effective than clonazepam. The anticonvulsant effect of clobazam in acoustically induced seizures in the mouse was less marked than those of clonazepam and diazepam as shown by ED50.

The exact mechanism of action of clobazam in the treatment of seizures is not fully understood and is generally thought to involve the potentiation of GABAergic neurotransmission, as a result of binding to the benzodiazepine site of the $GABA_A$ receptor. In *in vitro* studies, the half maximum inhibitory concentration at $GABA_A$ receptors was 0.3 nmol/L for clobazam and 30 nmol/L for diazepam. Unlike other benzodiazepines in clinical use, which have a 1,4-diazepine ring, clobazam has a 1,5-diazepine ring. In addition, clobazam is a partial agonist of the $GABA_A$ receptor, while the 1,4-benzodiazepines are full agonists. These differences between the compounds are generally considered to be the reason for the different pharmacodynamic properties observed between clobazam and other benzodiazepines.

**Pharmacokinetics**

**Absorption**

Mouth-dissolving or orodispersible tablets are designed to disintegrate/disperse within 3 minutes of putting the formulation in the mouth. In comparison, CLOBA MT tablets disintegrate within seconds as observed in in-vitro studies. Food has no significant effect on the absorption of clobazam.

**Distribution**

Clobazam is highly lipophilic and is rapidly distributed in fat and cerebral gray matter. Within 1 to 4 hours of administration it accumulates in the white matter and is then redistributed widely. The volume of distribution is large (≈100 L). Approximately 85% to 91% of clobazam is bound to plasma protein.

**Metabolism**

Clobazam is extensively metabolized in the liver. It undergoes dealkylation and hydroxylation before conjugation. Main metabolites found in plasma are N-desmethyl clobazam and 4-hydroxyclobazam. Lesser quantities of 4-hydroxy-N-desmethyl clobazam are also found.

**Excretion**

Clobazam is extensively metabolized, with minimal amounts recovered as the unchanged drug (≈2% of an administered dose in the urine and 1% in the feces). The main metabolic pathway is N-desmethylation, primarily by cytochrome P450 (CYP) 3A4, and to a lesser degree by CYP2C19 and CYP2B6.

The half-life of N-desmethyl clobazam is much longer (mean 42 hours; range 36-46 hours) than for that of clobazam (mean 18 hours; range 10-30 hours). The half-life of clobazam increases with the patient's age.

Therapeutic blood levels for clobazam are in the range of 50-300 ng/mL with the corresponding range for N-desmethylclobazam being from 1000-4000 ng/mL.

Pharmacokinetics in Special 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.

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

**Race:** There is no evidence of clinically significant effect of race on the clearance of clobazam.

**Renal Impairment:** Plasma concentrations of clobazam are reduced, possibly due to impaired absorption of the drug; terminal half-life is largely independent of renal function.

**Hepatic Impairment:** Hepatic disease may alter both the metabolism of the drug and its protein binding thus affecting plasma clobazam levels. In patients with severe liver disease, the distribution volume of clobazam is increased and the terminal half-life is prolonged.

**Indications**

CLOBA MT tablets are indicated for

- Adjunctive therapy in patients with epilepsy who are not adequately stabilized with their current anticonvulsant therapy
- Adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older
- Short-term management (2-4 weeks) of severe anxiety (for adults, and elderly)

**Dosage and Administration**

**Treatment of Epilepsy:**

Adults:

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

For doses above 5 mg/day administer in two divided doses. 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.

Pediatric patients aged 2 years and above:

| | ≤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 |

**Treatment of Anxiety:**

- Adults: 20-30 mg daily in divided doses or as a single dose given at night; maximum 60 mg daily
- Elderly: 10-20 mg daily; treatment requires low initial doses and gradual dose increments under careful observation.

**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 compared to adult dose presented in above table, 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.

**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 above table, 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.

**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 ESRD. It is not known if clobazam or its active metabolite, N-desmethylclobazam, is dialyzable.

**Dosage Adjustments in Patients with Hepatic Impairment:** CLOBA MT is hepatically metabolized; however, there are limited data to characterize the effect of hepatic impairment on the pharmacokinetics of CLOBA MT. 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 above table, 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 CLOBA MT in patients with severe hepatic impairment. Therefore no dosing recommendation in those patients can be given.

**Gradual Withdrawal:**

As with all antiepileptic drugs and benzodiazepines, withdraw CLOBA MT gradually. Taper by decreasing the total daily dose by 5-10 mg/day on a weekly basis until discontinued.

**Contraindications**

Clobazam is contraindicated in patients with the following conditions:

- Hypersensitivity to clobazam or any of its excipients;
- Myasthenia gravis (risk of aggravation of muscle weakness)
- Narrow angle glaucoma
- Any history of drug or alcohol dependence (increased risk of development of dependence)
- Severe respiratory insufficiency
- Sleep apnea syndrome (risk of deterioration)
- Severe impairment of liver function (risk of precipitating encephalopathy)
- During first trimester of pregnancy and breast-feeding

**Warnings and Precautions**

- Somnolence or Sedation: monitor for central nervous system (CNS) depression. Risk may be increased with concomitant use of other CNS depressants.
- Physical and Psychological Dependence: The risk of dependence is present even with use of clobazam 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 also increases in patients with a history of alcohol or drug abuse. Monitor patients with a history of substance abuse for signs of habituation and dependence.
- Withdrawal: Abrupt discontinuation of clobazam causes withdrawal symptoms. As with other benzodiazepines, CLOBA MT should be withdrawn gradually.

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- Serious Dermatological Reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis): discontinue CLOBA MT at first sign of rash unless the rash is clearly not drug-related.
- Suicidal Behavior and Ideation: monitor for suicidal thoughts or behaviors.
- Anterograde Amnesia: Anterograde amnesia is known to occur even if benzodiazepines are used in the normal dose range, but especially at higher dose levels. Amnesia effects may be associated with inappropriate behaviour.
- Increased Risk of Pneumonia: It is recognized that patients with epilepsy are at increased risk for aspiration due to recurrent seizures and that this risk is increased by the high co-morbidities seen in patients with LGS.
- Effects on Ability to Drive and Use Machines: Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.
- Tolerance: Loss of part or all of the anticonvulsant effectiveness of clobazam has been described in patients who have been receiving the drug for some time.
- Use in Patients with Acute or Chronic Respiratory Insufficiency: Clobazam can cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with clobazam.
- Use in Patients with Pre-existing Muscle Weakness or with Spinal or Cerebellar Ataxia: Clobazam can cause muscle weakness.
- Monitoring: If clobazam is administered for repeated cycles of therapy, periodic blood counts and liver, renal and thyroid function tests are advisable.

**Pregnancy and Lactation**

Pregnancy category C.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become pregnant or suspects that she is pregnant.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate such as hypothermia, hypotonia, moderate respiratory depression and difficulties in drinking (signs and symptoms of so-called "floppy infant syndrome"), can be expected due to the pharmacological action of the compound.

Moreover, infants born to mothers who took benzodiazepines during the latter stage of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Appropriate monitoring of the newborn in the postnatal period is recommended.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Carcinogenesis

The carcinogenic potential of clobazam has not been adequately assessed. In a limited study in rats, oral administration of clobazam (4, 20, and 100 mg/kg/day) for 2 years resulted in an increased incidence of thyroid follicular cell adenomas in males at the high dose.

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 study in which clobazam (50, 350, or 750 mg/kg/day) 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.

**Adverse Effects**

In clinical studies in epilepsy patients, adverse events were reported in about 33% of patients with most frequently reported events being drowsiness, dizziness and fatigue.

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

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

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

Tolerance and dependence may develop, especially during prolonged use.

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

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

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

Clobazam may cause respiratory depression, especially if administered in high doses. Therefore, particularly in patients with pre-existing compromised respiratory function (e.g. in patients with bronchial asthma) or brain damage, respiratory insufficiency may occur or deteriorate. Reports of aspiration pneumonia and pneumonia have been reported with the use of clobazam.

**Drug Interactions**

Effects of CLOBA MT on other drugs:

- Hormonal Contraceptives: CLOBA MT is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with CLOBA MT.
- Drugs metabolized by CYP2D6: Lower doses of these drugs may be required when used concomitantly with CLOBA MT.

Effects of other drugs on CLOBA MT

- Strong or Moderate CYP2C19 Inhibitors: Dosage adjustment of CLOBA MT may be necessary.
- Alcohol: Increases blood levels of clobazam by about 50%.

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

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

Pharmacodynamic interaction:

- CNS Depressants and Alcohol: Concomitant use of CLOBA MT with other CNS depressants may increase the risk of sedation and somnolence.

**Overdosage**

**Signs and Symptoms of Overdosage**

Overdose and intoxication with benzodiazepines, including CLOBA MT, 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 alcohol.

**Management of Overdosage**

The management of CLOBA MT 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 CLOBA MT 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.

**Storage**

Store at room temperature, protected from light and moisture.

**Presentation**

CLOBA MT 5 & 10 are available in strip of 10 Tablets.

Manufactured by:

INTAS

***INTAS PHARMACEUTICALS LTD.***

Samardung Road, Kabrey Block, Namthang Elaka,
South Sikkim-737132, INDIA

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Size : 140 x 210 (mm) Back Side
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