Nucloba 5 10 Tablet

1. **Generic Name**

   Clobazam

2. **Qualitative and Quantitative Composition**

Clobazam 5/10mg

3. **Dosage form and strength**

Oral tablets containing clobazam 5/ 10 mg.

4. **Clinical particulars**

4.1 Therapeutic indication

Nucloba is indicated for treatment of acute and chronic anxiety and as adjuvant in patients with refractory epilepsy.

4.2 Posology and method of administration

- **Treatment of anxiety**

The usual anxiolytic dose for adults is 20-30mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety.

The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced.

It should not be used for longer than 4 weeks. Long term chronic use as an anxiolytic is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise.

- Treatment of epilepsy in association with one or more other anticonvulsants

Adults: In epilepsy a starting dose of 20-30mg daily is recommended, increasing as necessary up to a maximum of 60mg daily.

When prescribed for children treatment requires low initial doses and gradual dose increments under careful observation. It is recommended that normally treatment should be started at 5mg daily. A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendations can be made in children under 6 years of age.

4.3 Contraindication

Nucloba Tablets must not be used:

- In patients with hypersensitivity to benzodiazepines or any of the excipients of Nucloba.
- In patients with any history of drug or alcohol dependence (increased risk of development of dependence).
- In patients with myasthenia gravis (risk of aggravation of muscle weakness).
- In patients with severe respiratory insufficiency (risk of deterioration).
- In patients with sleep apnoea syndrome (risk of deterioration).
- In patients with severe hepatic insufficiencies (risk of precipitating encephalopathy).
- During the first trimester of pregnancy.
- In breast-feeding women.

Benzodiazepines must not be given to children without careful assessment of the need for their use. Clobazam must not be used in children between the ages of 6 months and 3 years, other than in exceptional cases for anticonvulsant treatment where there is a compelling indication. As there is no age appropriate formulation to enable safe and accurate dosing, no dosage recommendations can be made in children under 6 years of age

4.4 Special warnings and precautions for use

- Amnesia

Amnesia may occur with benzodiazepines. In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines. Special caution is necessary if Clobazam is used in patients with myasthenia gravis, spinal or cerebellar ataxia or sleep apnoea. A dose reduction may be necessary.

• Muscle weakness

Clobazam can cause muscle weakness. Therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea, special observation is required and a dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis.

• Depression and personality disorders

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

• Dependence

Use of benzodiazepines - including Clobazam - may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. Therefore the duration of treatment should be as short as possible.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (or rebound phenomena). Rebound phenomena are characterised by a recurrence in enhanced form of the symptoms which originally led to Clobazam treatment. This may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness.

A withdrawal syndrome may also occur when abruptly changing over from a benzodiazepine with a long duration of action (for example, Clobazam) to one with a short duration of action.

• Serious Skin Reaction

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 post marketing experience. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs that are associated with serious skin reactions. SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered

• Respiratory Depression

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of Clobazam may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (please refer to section 4.3 Contraindications).

- Alcohol

It is recommended that patients abstain from drinking alcohol during treatment with Clobazam.

4.5 Drug interactions

- 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.

- CNS Depressants and Alcohol

Concomitant use of Nucloba with other CNS depressants may increase the risk of sedation and somnolence

- Effect of Nucloba on Other Drugs

Hormonal Contraceptives

Nucloba is a weak CYP3A4 inducer. As some hormonal contraceptives are metabolized by CYP3A4, their effectiveness may be diminished when given with Nucloba. Additional non-hormonal forms of contraception are recommended when using Nucloba.

Drugs Metabolized by CYP2D6

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

- Effect of Other Drugs on NUCLOBA

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 Nucloba may be necessary when co-administered with strong CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, ticlopidine) or moderate CYP2C19 inhibitors (e.g., omeprazole).

4.6 Use in special population

- Pediatric: Safety and effectiveness in patients less than 2 years of age have not been established.
- Geriatric: Clinical studies 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 10-20 mg/day. Patients may be titrated further to a maximum daily dose of 40 mg if tolerated
- Liver impairment: Lower doses are recommended.

- Renal failure: No dose adjustment is required for patients with mild and moderate renal impairment. There is essentially no experience with Nucloba in patients with severe renal impairment or ESRD.
- Pregnancy and lactation: Pregnancy Category C. There are no adequate and well-controlled studies of Nucloba in pregnant women. In animal studies, administration of Clobazam during pregnancy resulted in developmental toxicity, including increased incidences of fetal malformations, at plasma exposures for Clobazam and its major active metabolite, N-desmethylclobazam, below those expected at therapeutic doses in patients. Nucloba should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

  Nucloba is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Nucloba, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machine

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. Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Nucloba is known.

4.8 Undesirable effects

Thrombocytopenia, Tachycardia, Bradycardia, Vertigo, Diplopia, Vomiting, Constipation, Nausea, Weight increased , Decreased appetite , Muscular weakness , Aggression, Insomnia, Irritability, Abnormal behaviour, Dyspnoea, Rash, Pruritus, Hypotension

4.9 Overdose

- Signs and Symptoms of Overdosages

Overdose and intoxication with benzodiazepines, including Nucloba, 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 Overdosages

The management of Nucloba 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 Nucloba 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 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 GABAA receptor.

5.2 Pharmacodynamic properties

- 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% cNuclobadence 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, Nucloba did not prolong the QTc interval to any clinically relevant extent.

5.3 Pharmacokinetic properties

- Absorption

Clobazam is rapidly and extensively absorbed following oral administration. The time to peak concentrations (Tmax) 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 Tmax ranged from 0.5 to 2 hours.

- 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 80-90% 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 3-5 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 asingle oral dose of radiolabelled 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. 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

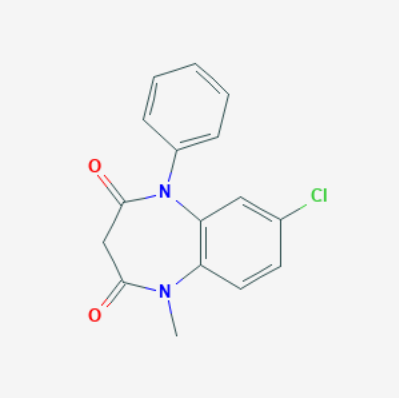
Oral administration of clobazam (0, 10, 30, or 75 mg/kg/day) to pregnant rabbits throughout the period of organogenesis resulted in decreased fetal body weights, and increased incidences of fetal malformations (visceral and skeletal) at the mid and high doses, and an increase in embryofetal mortality 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.

7. Description

Clobazam is a 1,5-benzodiazepine and partial gamma-aminobutyric acid (GABA) receptor agonist, with anxiolytic, sedative, and anticonvulsant activities. Clobazam binds to a specific site, distinct from the inhibitory neurotransmitter GABA binding site, on the benzodiazepine-GABA-A-chloride ionophore receptor complex located in the central nervous system (CNS). This binding causes an allosteric modification of the receptor and enhances the affinity of GABA to the receptor leading to an increase in the opening of chloride-channels. This leads to an increase in chloride ion conductance, neuronal hyperpolarization, inhibition of the action potential and a decrease in neuronal excitability.

Clobazam is a DEA Schedule IV controlled substance. Substances in the DEA Schedule IV have a low potential for abuse relative to substances in Schedule III. Clobazam is a benzodiazepine that is used as an anticonvulsant in the therapy of severe childhood epilepsy. Therapy with clobazam has not been associated with serum aminotransferase elevations, and clinically apparent liver injury from clobazam has yet to be reported and must be rare, if it occurs at all.



.

8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life

24 months.

8.3 Packaging Information

Nucloba is available in the pack of 10 tablets.

8.4 Storage and handling instructions

Store Nucloba tablets in a dry place

9. Patient Counselling Information

9.1 Adverse Reactions

Refer part 4.8

9.2 Drug Interactions

Refer part 4.5

9.3 Dosage

Refer part 4.2

9.4 Storage

Refer part 8.4

9.5 Risk Factors

Refer part 4.4

9.6 Self-monitoring information

NA

9.7 Information on when to contact a health care provider or seek emergency help

Patients are advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications

Refer part 4.3

10. Manufactured by THE MADRAS PHARMACEUTICALS

11. Details of permission or license number with date

LIC NO.247, - 13.11.1989

12. Date of revision: January 2022