Nucloba 5 10 Tablet

1. **Composition**

Clobazam 5/10mg

2. **Dosage form and strength**

Nucloba is available in 10 tablets.

3. **Clinical particulars**

3.1 Therapeutic indication

Nucloba is indicated as:

- Add on therapy in treatment of seizures
- As main therapy if patient intolerant/resistant to first line antiepileptic therapy
- Also in treatment of:

✓ Partial (focal) and generalised seizures
✓ Status epilepticus
✓ Febrile seizures
✓ Lennox Gastaut Syndrome(LGS)

3.2 Posology and method of administration

Recommended oral dose of Nucloba is:

- Paediatric patients- 0.25mg/kg body weight daily
- Adult patients-

✓ Start with 10 mg and down titrate as per the need(Efficacy and Safety)

OR

✓ Start with 5 mg and up/down titrate as per the need (Efficacy and Safety)

3.3 Contraindication

Nucloba is contraindicated in patients with a history of hypersensitivity to the drug or its ingredients.

3.4 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.

3.5 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

<u>Hormonal Contraceptives</u>

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.

<u>Drugs Metabolized by CYP2D6</u>

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

- Effect of Other Drugs on NUCLOBA

<u>Strong and moderate inhibitors of CYP2C19</u>

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).

3.6 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.

3.7 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.

3.8 Undesirable effects

The side effects of Clobazam are generally mild and usually disappear if the dose is reduced. They may also go away over time as a person gets used to the medicine. The side effects most often reported are:

- Drowsiness

- Dizziness
- Poor coordination
- Drooling
- Restlessness or aggressiveness

3.9 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.

4. Pharmacological properties

4.1 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.

4.2 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.

4.3 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 a single 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.

5. Nonclinical properties

5.1 Animal Toxicology or Pharmacology

Not required.

6. Description

Already mentioned and covered in the above points.

7. Pharmaceutical particulars

7.1 Incompatibilities

There are no known incompatibilities.

7.2 Shelf-life

24 months.

7.3 Storage and handling instructions

Store in a cool, dry place, away from direct heat and light. Keep out of the reach and sight of children.