1 INDICATIONS AND USAGE

Clobazam Tablets are 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

Clobazam tablets can be administered whole, broken in half along the score, or crushed and mixed in a small amount of food. Clobazam tablets are not bioequivalent when administered with food. Therefore, the dosing information is based on administration of tablets without food. The QT interval should be monitored in patients receiving multiple dose regimens or high doses of clobazam.

2.2 Recommended Dosage

Table 1: Recommended Dosing (500 mg as the Base)

| Weight | Recommended Dose | Maximum Dose
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2-20 kg</td>
<td>0.5-2 mg/day</td>
<td>4 mg/day</td>
</tr>
<tr>
<td>21-30 kg</td>
<td>1-4 mg/day</td>
<td>8 mg/day</td>
</tr>
<tr>
<td>&gt;30 kg</td>
<td>5-10 mg/day</td>
<td>20 mg/day</td>
</tr>
</tbody>
</table>

2.3 Titrating Clobazam

Clobazam tablets should be titrated to the minimum dose required to achieve clinical efficacy and tolerability. Each dose in Table 1 (e.g., 5 to 20 mg in ≤30 kg weight) is intended as a guideline. The maximum dose (20 mg/day or 40 mg/day, depending on weight) may be started on the day of initiation of clobazam. Patients should be titrated to the maximum dose tolerated and the minimum dose required for control of seizures.

2.5 Dosage Adjustments in CYP2C19 Poor Metabolizers

Patients with CYP2C19 polymorphisms who are poor metabolizers of CYP2C19 may require higher doses of clobazam to achieve the same plasma concentrations as extensive metabolizers. Dose adjustments may be necessary based on clinical response and plasma concentration monitoring.

2.7 Dosage Adjustments in Patients with Hepatic Impairment

Dose adjustments should be made with caution in patients with hepatic impairment. Clobazam is primarily metabolized by CYP2C19 and therefore dose adjustments may be necessary in patients with hepatic impairment.

3 CLINICAL PHARMACOLOGY

3.1 Mechanism of Action

Clobazam is a benzodiazepine that increases the efficacy of the GABAergic neurotransmitter system. It has a high affinity for the benzodiazepine receptor site on the gamma-aminobutyric acid (GABA) receptor complex, which modulates chloride ion currents, leading to an increase in inhibitory neurotransmission.

3.3 Pharmacokinetics

Clobazam is rapidly absorbed following oral administration, with peak plasma concentrations achieved within 1-4 hours. The mean peak concentration is approximately 1-2 mg/L. The half-life of clobazam is about 20 hours, and it is extensively metabolized by the liver. The major metabolite is n-desmethylclobazam, which is also active as a benzodiazepine.

4 ADVERSE REACTIONS


<table>
<thead>
<tr>
<th>Event</th>
<th>All %</th>
<th>N=179</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Delirium</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Delusion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hallucination</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

5.4 Withdrawal Symptoms

Clobazam should not be withdrawn abruptly. Abrupt withdrawal can result in seizures that will not stop (status epilepticus), neuroleptic malignant syndrome, and serotonin syndrome. Therefore, clobazam should be tapered slowly over a period of weeks to months depending on the duration of therapy and the severity of the underlying condition. If clobazam is tapered too rapidly, seizures may occur. If stopping clobazam suddenly is unavoidable, patients should be monitored closely for seizures and other withdrawal symptoms.

8.6 CYP2C19 Poor Metabolizers

CYP2C19 is a phase 1 drug metabolizing enzyme. A fraction of the population (estimated at 5-10%) is CYP2C19 poor metabolizers. CYP2C19 poor metabolizers tend to have a slower metabolism of clobazam and therefore require higher doses to achieve the same plasma concentrations as extensive metabolizers.

9.1 Pregnancy

Clobazam is excreted in human milk. Postmarketing experience suggests that clobazam is present in breast milk at concentrations that may be harmful to the infant. Mothers should be counselled about the risks and benefits of breastfeeding while taking clobazam.

9.4 Radiation Exposures

Clobazam is a category B drug during pregnancy. Animal studies have not been conducted to evaluate the effects of clobazam on reproduction. However, category B drugs are believed to be safe for use during pregnancy, but there is insufficient data to confirm this. Therefore, clobazam should be used during pregnancy only if benefit outweighs risk.

10 OVERDOSAGE

10.2 Management of Overdosage

Treatment of clobazam overdose should include supportive and symptomatic measures. Clobazam is not removed by hemodialysis or peritoneal dialysis. Activated charcoal is not expected to have a significant role in clobazam overdose.

11 CONCERNS AND PREGNANCY

11.2 Prenatal and Neonatal Development

Animal studies have not been conducted to evaluate the effects of clobazam on pre- and post-natal development. However, category B drugs are believed to be safe for use during pregnancy, but there is insufficient data to confirm this. Therefore, clobazam should be used during pregnancy only if benefit outweighs risk.

12.3 Pharmacokinetics

Clobazam is rapidly metabolized by the liver and excreted in the urine. The major metabolite is n-desmethylclobazam, which is also active as a benzodiazepine. Clobazam is eliminated from the body primarily by renal excretion.

12.4 Teratogenic Effects

There is no information on the effects of clobazam on embryo-fetal development in human. However, animal studies have not been conducted to evaluate the effects of clobazam on embryo-fetal development. Therefore, clobazam should be used during pregnancy only if benefit outweighs risk.

12.5 Nursing Mothers

Clobazam is excreted in human milk. Postmarketing experience suggests that clobazam is present in breast milk at concentrations that may be harmful to the infant. Mothers should be counselled about the risks and benefits of breastfeeding while taking clobazam.

13.1 Information for Patients

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

13.2 Information for Healthcare Providers

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.1 Information about Addictive Substances

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.2 Information about Antidepressant Use

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.3 Information about Alcohol Use

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.4 Information about Other Medications

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.5 Information about Other Substance Use

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.

14.6 Information about Discontinuation

Clobazam is a benzodiazepine that can cause sedation, drowsiness, and other central nervous system effects. Patients should be advised to avoid driving and operating machinery until they are familiar with the drug's effects on them.
The polymorphic CYP2C19 is the main enzyme that metabolizes the pharmacologically active metabolites of clobazam. Population pharmacokinetic analysis showed that the elimination of clobazam is largely dependent on the expression of CYP2C19, which is influenced by genetic variability. This variability may lead to differences in plasma concentrations of clobazam, potentially affecting its therapeutic and side effects. Genotyping for CYP2C19 may be considered to optimize individualized therapy and reduce the risk of adverse drug reactions. Patients with a lower CYP2C19 activity may require a lower initial dose, while patients with higher CYP2C19 activity may tolerate a higher initial dose, allowing for better drug efficacy and safety. Further research is needed to fully understand the genetic and pharmacological implications of CYP2C19 in clobazam metabolism and to develop personalized dosing strategies.