

Clonazepam

Brand name: Klonopin, Rivotril



Drug monograph

Pharmacology

Anticonvulsant

Clonazepam's pharmacological profile is similar to other anxiolytic/sedative benzodiazepines. Its basic anticonvulsive properties are also similar to those of other diazepines. Clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

Clonazepam is well absorbed orally with maximum blood concentrations occurring in 1 to 2 hours. Clonazepam is metabolized by the liver to inactive metabolites, which are excreted mainly in the urine. Less than 0.5% of a dose is excreted in the urine unchanged and from 9 to 27% of a dose may be excreted in the feces. The half-life of the parent compound varies from approximately 18 to 50 hours.

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Indications

Alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome). May also be of some value in patients with absence spells (petit mal) who have failed to respond to succinimides.

Up to nearly 33% of the patients in some studies have shown a loss of anticonvulsant activity, often within the first 3 months of clonazepam administration. In some cases, dosage adjustment may re-establish efficacy.

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Contraindications

Significant liver disease, narrow angle glaucoma, sensitivity to benzodiazepines.

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Warnings

Pregnancy:

Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased 2 to 3 fold. The increase is largely due to specific defects, e.g., congenital malformations of the heart, and cleft lip and/or palate.

Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to phenytoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsants, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g., genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsants should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risk of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of childbearing age should be encouraged to seek professional counsel and should report the onset of pregnancy promptly to their physician. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

In a reproductive study in rabbits, clonazepam administration was associated with an increased incidence of cleft palate and other anomalies at 2 dose concentrations. Accordingly, clonazepam should be used in women of childbearing potential only when the expected benefits to the patient warrant the possible risk to a fetus.

Lactation:

Mothers receiving clonazepam should not breast feed their infants.

Children:

Because of the possibility that adverse effects on childhood physical or mental development could become apparent only after years, a risk-benefit consideration of the long-term use of clonazepam is important in pediatric patients.

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Precautions

Although simultaneous administration of several anticonvulsants may be considered with clonazepam, such combined therapy may result in an increase of central depressant adverse effects. In addition, the dosage of each drug may be required to be adjusted to obtain the optimum effect.

Abrupt withdrawal of clonazepam particularly in those patients on long-term, high dose therapy, may precipitate status epilepticus. Therefore, as with any other anticonvulsants, gradual withdrawal is essential when discontinuing clonazepam. While clonazepam is being gradually withdrawn, the simultaneous substitution of incremental doses of another anticonvulsant may be indicated.

A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during clonazepam treatment. When used in patients in whom several different types of seizures coexist, clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). These phenomena may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam may produce absence status.

Occupational Hazards:

Caution patients receiving clonazepam against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle.

They also should be warned against the concomitant use of alcohol and other CNS depressant drugs.

The CNS depressant action of benzodiazepines may be potentiated by other drugs such as alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, anxiolytics, phenothiazines, thioxanthene and butyrophenone antipsychotic agents, MAO inhibitors and tricyclic antidepressants.

Benzodiazepines have produced habituation, dependence and withdrawal symptoms similar to those noted with barbiturates and alcohol. Therefore, patients who may be prone to increasing the dose of drugs on their own initiative should be under careful monitoring when receiving clonazepam.

Periodic liver function tests and blood counts are recommended during long-term clonazepam therapy.

Clonazepam and its metabolites are excreted by the kidneys; to avoid excessive accumulation, exercise caution in administering the drug to patients with impaired renal function.

Hypersecretion in the upper respiratory passages has at times been a troublesome adverse reaction during clonazepam therapy, especially in small mentally retarded children who ordinarily have difficulty handling secretions. Treatment with clonazepam should be instituted with caution in patients with chronic respiratory diseases.

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Adverse Effects

The most frequently occurring adverse reactions to clonazepam are referable to CNS depression. Drowsiness occurs in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time. Behaviour problems have been noted in approximately 25% of patients and increased salivation in 7%.

Others, listed by system, are:

CNS:

Alterations in behaviour, which have been variously reported as aggressiveness, argumentative behaviour, hyperactivity, agitation, depression, euphoria, irritability, forgetfulness and confusion. These behavioural reactions are particularly likely to occur in patients with a prior history of psychiatric disturbances and are known to occur in patients with chronic seizure disorders.

Other adverse reactions involving the CNS have included nystagmus, unsteady gait, slurred speech, dysarthria, vertigo, insomnia, and diplopia. Isolated reports of akinesia, hemiparesis, tremor, hypotonia, headache and choreiform movements have been received. Minor changes in EEG patterns specifically low-voltage fast activity.

Gastrointestinal:

Increased salivation, nausea, vomiting, anorexia, constipation, diarrhea, encopresis, dry mouth, increased appetite, abdominal pain, hepatomegaly.

Genitourinary:

Rare instances of dysuria, nocturia, incontinence, urinary retention, enuresis.

Integumentary:

Nonspecific erythematous, papular and maculopapular rashes, swelling of the face and eyelids, urticaria, pruritus. Hirsutism and hair loss have also been reported, but drug relationship has not been established.

Musculoskeletal:

Muscle weakness, low back pain.

Respiratory:

Hypersecretion in the upper respiratory passages, rhinorrhea, dyspnea, respiratory depression.

Hematopoietic:

Anemia, leukopenia (WBC below 4000/mm³), thrombocytopenia, eosinophilia.

Liver function:

Slight, transient elevations of transaminase and alkaline phosphatase.

Miscellaneous:

Palpitations, coated tongue, dehydration, fever, lymphadenopathy, weight gain or loss, changes in libido, gynecomastia, hallucinations, dysdiadochokinesis, coma, aphonia.

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Overdose

Symptoms:

The cardinal manifestations of overdosage are drowsiness and confusion, reduced reflexes and coma. There are minimal effects on respiration, pulse and blood pressure, unless the overdosage is extreme. Patients have recovered from dosages of up to 60 mg without special treatment. When the effects of the drug overdosage begin to wear off, the patient exhibits some jitteriness and over stimulation.

Treatment:

Gastric lavage may be beneficial if performed soon after ingestion of clonazepam. Supportive measures should be instituted as indicated: maintenance of an adequate airway, i.v. fluids and monitoring of pulse, blood pressure and respiration. CNS stimulants and vasopressors may be used if necessary. Dialysis appears to be of no value.

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Dosage

Must be determined individually according to clinical response and tolerance and depends primarily on the patient's age.

Children:

In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg) should be between 10 and 30 mcg/kg/day and should not exceed 50 mcg/kg/day given in 2 or 3 divided doses. Dosage should be increased by no more than 250 to 500 mcg every third day until a maintenance dose of 100 to 200 mcg/kg has been reached, unless seizures are controlled or adverse effects preclude further increase.

Whenever possible, the daily dose should be divided into 3 equal doses. If doses are not equally divided, the larger dose should be given before retiring.

Adults:

The initial adult dose should not exceed 1.5 mg/day divided into 3 doses. Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until adverse effects preclude any further increase. Maintenance dosage

must be individualized for each patient depending upon response. A recommended adult maintenance dose is 8 to 10 mg/day in 3 divided doses. Dosages in excess of 20 mg/day should be administered with caution.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be borne in mind whenever clonazepam is added to an already existing anticonvulsant regimen.

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Supplied

0.5 mg:

Each cylindrical, biplane, scored tablet, edges bevelled, contains: Clonazepam 0.5 mg (orange, with {RIVOTRILover0.5} engraved on one face, single-scored on the other with ROCHE above and C below score). Also contains lactose, microcrystalline cellulose, cornstarch, sunset yellow FCF aluminum lake, magnesium stearate.

2 mg:

Each cylindrical, biplane, scored tablet, edges bevelled, contains: Clonazepam 2 mg (white, with {ROCHEover2} engraved on one side and cross-scored on the other). Also contains lactose, microcrystalline cellulose, cornstarch, magnesium stearate.

Energy: 2.4 kJ (0.6 kcal). Gluten-free, paraben-free, sodium-free, sulfite-free and tartrazine-free. Bottles of 100 and 500. Keep in a tightly closed, light-resistant container. Store at 15 to 30°C.

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