PRESCRIBING INFORMATION

For the use of a registered medical practitioner or hospital or laboratory only

ZAPIZ 0.25 / 0.5 / 1 / 2

(Clonazepam Melt-in-Mouth Tablets 0.25 mg / 0.50 mg / 1 mg / 2 mg)

COMPOSITION

ZAPIZ 0.25

Each melt-in-mouth tablet contains
Clonazepam 0.25 mg

ZAPIZ 0.5

Each melt-in-mouth tablet contains
Clonazepam 0.50 mg

ZAPIZ 1

Each melt-in-mouth tablet contains
Clonazepam 1 mg

ZAPIZ 2

Each melt-in-mouth tablet contains
Clonazepam 2 mg

DESCRIPTION

Clonazepam is a benzodiazepine compound. Chemically, clonazepam is 5-(*O*-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. The molecular formula of clonazepam is $C_{15}H_{10}ClN_3O_3$ and molecular weight 315.72. Its structural formula is as under (figure 1).

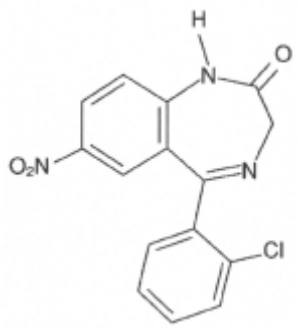

Figure 1. Clonazepam ($C_{15}H_{10}ClN_3O_3$ = 315.72)

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Its antiseizure and antipanic effects are thought to be related to its ability to enhance the activity of gamma aminobutyric acid in the neurons of the CNS. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, 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.

PHARMACOKINETICS

Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

INDICATIONS

(1) Seizure Disorders:
Clonazepam is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures, also in patients with absence seizures (petit mal) who have failed to respond to succinimides;
(2) Panic Disorder:
Clonazepam is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV.

CONTRAINDICATIONS

Clonazepam should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

DOSAGE AND ADMINISTRATION

(1) Seizure Disorders

Adults: Initial dose: 1.5mg/day in 3 divided portions; increments of 0.5-1mg every 3 days until adequate seizure control or side effects appear; maximum adult dose: 20mg/day; maintenance dosage: individualized for each patient depending upon response.
Pediatric Patients: Initial dosage (up to 10 yrs / 30 Kg): 0.01-0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in 2 or 3 divided doses; dosage should be increased by no more than 0.25 to 0.5 mg every 3rd day until a daily maintenance dose of 0.1 to 0.2 mg/kg or seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into 3 equal doses.

(2) Panic Disorder
Adults: The initial dose is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. Some individual patients may benefit from doses of up to a maximum of 4 mg/day, and in them the dose may be increased in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable. Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.

WARNINGS AND PRECAUTIONS

General:
Clonazepam may impair cognitive and motor performance – patients to be cautioned against driving, operating machinery, or other activities requiring full mental alertness and intact reflexes.
Worsening of seizure may occur when used in patients in whom several types coexist – esp. generalized tonic-clonic seizures may be precipitated.
Gradual withdrawal after long-term use is essential to avoid status epilepticus.
May cause excess salivation.

Renal impairment:
Clonazepam metabolites may accumulate, dosage modification may be needed.

Hepatic impairment:
Dosage modification may be needed.

Pregnancy:
Pregnancy category D
Benzodiazepines, including clonazepam, are known to have teratogenic potential. Use of clonazepam during the 1st trimester must be avoided. Use of clonazepam during known pregnancy should be considered only when the clinical situation warrants the risk to the fetus. Patients must notify their physician if they become pregnant or intend to become pregnant during therapy with clonazepam.

Labor and Delivery:
Perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena.

Lactation:
Mothers taking clonazepam should avoid breast-feeding.

Pediatric Use:
Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam is important in pediatric patients being treated for seizure disorder.

Geriatric Use:
Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenicity studies have not been conducted with clonazepam.
The data currently available are not sufficient to determine the genotoxic potential of clonazepam.
In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

ADVERSE REACTIONS

In seizure disorder patients

Prominent side effects are: drowsiness (50% of patients), and ataxia (30% of patients) – these may diminish with time; also, behavioral problems (25% of patients).

In panic disorder patients

Prominent side effects are: somnolence, depression, dizziness, nervousness, ataxia, and reduced intellectual ability.

Other side effects, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, “glassy-eyed” appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo
Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis, suicidal attempt (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams
Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages
Cardiovascular: Palpitations
Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema
Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums
Genitourinary: Dysuria, enuresis, nocturia, urinary retention
Musculoskeletal: Muscle weakness, pains
Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia
Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

DRUG INTERACTIONS

Clonazepam does not alter pharmacokinetics of phenytoin, carbamazepine or barbiturates; but they induce CYP450 and reduce clonazepam plasma concentration by 30%. Fluoxetine has no effect on clonazepam pharmacokinetics. Oral antifungals to be used with caution. Its CNS depressant actions can be potentiated by alcohol and other CNS depressants.

DRUG ABUSE AND DEPENDENCE

Clonazepam is a Schedule X controlled substance.

Physical and Psychological Dependence:
Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam.

OVERDOSAGE

Symptoms of clonazepam overdosage include somnolence, confusion, coma and diminished reflexes.

Overdose Management:
Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value. Flumazenil, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines.

PRESENTATION
ZAPIZ 0.25:
ZAPIZ 0.5:
ZAPIZ 1:
ZAPIZ 2:

STORAGE
Store in a cool and dry place at a temperature below 30°C.
Keep all medicines away from the reach of children.

MANUFACTURED BY
INTAS PHARMACEUTICALS LIMITED
SIKKIM.

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