PRODUCT MONOGRAPH

Zym-CLONAZEPAM

(Clonazepam Tablets USP)

0.25mg , 0.5 mg, 1.0 mg and 2.0 mg

Anticonvulsant

Zymcan Pharmaceuticals Inc.
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Date of Preparation
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Control # 118488

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Zym-CLONAZEPAM

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THERAPEUTIC CLASSIFICATION

Anticonvulsant

ACTIONS AND CLINICAL PHARMACOLOGY

Clonazepam has pharmacological properties characteristic of the benzodiazepine class of drugs. Clonazepam has sedative, hypnotic and anticonvulsant properties. As an anticonvulsant it is useful in the management of minor motor seizures (myoclonic seizures) and may be of some value in selected patients with absence spells (petit mal) who have failed to respond to succinimides.

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. Single oral doses of clonazepam to healthy volunteers gives maximum blood levels of drug, in 1 to 3 hours. The half-life of the parent compound ranges from approximately 18 to 50 hours. The major route of excretion of clonazepam is the urine. A comparative bioavailability study was performed using normal human volunteers. The rate and extent of absorption after a single oral dose of the test product clonazepam 2 mg manufactured by Zymcan Pharmaceuticals Inc., vs. the reference product Rivotril 2 mg manufactured by Hoffman Laroche was measured and compared. The results can be summarized as follows:

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

	GEOMETRIC MEAN ARITHMETIC MEAN (C.V.)		
PARAMETERS	TEST - 2.0mg	REFERENCE - 2.0mg	RATIO
AUC_t (ng.hr/mL)	392.02 398.22 (17.48)	364.95 372.26 (19.86)	107.42%
AUC (ng.hr/mL)	459.71 466.40 (16.84)	428.70 434.63 (16.70)	107.23%
C_{max} (ng/mL	10.56 10.71 (15.90)	10.03 10.21 (19.19)	105.33%
T_{max} * (hours)	2.57 (1.81)	2.56 (2.31)	---------
$T_{1/2}$el * (hours)	35.93 (7.32)	34.06 (7.06)	----------

* For the Tmax and $T_{1/2}$el parameters these are the arithmetic means with standard deviation in parenthesis.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Zym-Clonazepam 0.5 mg Tablets (Lot # 640381) versus

Rivotril 0.5 mg Tablets, Hoffman-La Roche Ltd., Canada (Lot # 93390 B)

2 mg (4 x 0.5 mg) oral administration in the fasting state

Measured Data

Parameter	Test	Geomtric Mean Arithmetic Mean (C.V.%) Reference	Ratio of Means (%) (90% of Confidence Limits)
AUC_{0-72h} (ng.h/mL)	272.35 276.82 (17.1)	261.83 265.88 (18.0)	104.0 (98.5 - 109.8)
AUC_T (ng.h./mL)	328.96 337.02 (20.2)	302.50 308.80 (20.4)	108.8 (101.7 - 116.3)
AUC_∞ (ng.h/mL)	410.96 421.20 (21.0)	375.80 382.72 (19.1)	109.4 (101.2 - 118.1)
C_{max} (ng/mL)	8.64 8.74 (16.6)	7.85 7.97 (18.4)	110.1 (104.5 - 115.9)
T_{max} (h)	1.94 (0.73)	2.60 (1.42)	---
$T1/2_{el}$ (h)	47.77 (11.7)	42.39 (16.8)	---

For the T_{max} and $T1/2_{el}$ parameters these are the arithmetic means with standard deviation in parenthesis.

INDICATIONS AND CLINICAL USE

Clonazepam has been found useful when used alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome).

Clonazepam may be of some value in patients with absence spells (petit mal) who have failed to respond to succinimides.

Tolerance to the anticonvulsant effect of clonazepam has been shown to occur in approximately 30% of patients. Loss of efficacy has often developed within the first 3 months of drug administration. The development of tolerance has been shown to vary according to the seizure type. In some cases dosage adjustments or temporary withdrawal of treatment followed by re-introduction of the drug may establish efficacy.

CONTRAINDICATIONS

Zym-CLONAZEPAM should not be used in patients with a history of sensitivity to benzodiazepines. Clonazepam is also contraindicated in patients with clinical or biochemical evidence of significant liver disease and in patients with narrow angle glaucoma.

WARNINGS

Use in Pregnancy: 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 two to three-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 medication deliver normal infants. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, 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.

Anticonvulsant drugs should not be discontinued in patients with 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 anti-epileptic medication is in doubt, appropriate consultation might be indicated.

In a reproductive study in rabbits, administration of clonazepam was associated in a dose- dependent manner with an increased incidence of cleft palate and other anomalies (see Teratology and Reproduction Studies).

The preceding considerations should be borne in mind and clonazepam should be used in women of child-bearing potential only when the expected benefits to the patient warrant the possible risk to the fetus. Mothers receiving clonazepam should not breast feed their infants.

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

PRECAUT1ONS

Co-administration of clonazepam with other anticonvulsants may be considered, however this may result in an increase in central depressant adverse effects. In addition, the dosage adjustment of other anticonvulsants may be necessary to obtain the optimal effect. In order to maintain seizure control, when clonazepam is used to replace other anticonvulsant therapy, the dosage of clonazepam should be gradually increased while the dosage of the other medication is gradually decreased; when clonazepam is used to supplement other anticonvulsant therapy, the dosage of clonazepam should be gradually increased until seizure activity is adequately controlled. Then the dosage of the other medication may then be gradually decreased if necessary.
In addition, clonazepam should be withdrawn gradually, especially in those patients on long- term, high-dose therapy, since abrupt withdrawal may precipitate seizures or status epilepticus During

withdrawal of clonazepam, the simultaneous administration of another anticonvulsant may be indicated. Exacerbation in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with clonazepam. 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 dosage. Conflicting reports exist on the association between absence status and the concomitant use of valproic acid and clonazepam in seizure patients. However no recommendation can be made on the combination of valproic acid and clonazepam until further studies are available.

Patients receiving clonazepam should be cautioned 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 central nervous system depressant action of the benzodiazepine class of drugs may be potentiated by other drugs such as alcohol, narcotics, barbiturates, non-barbiturate hypnotics, anti-anxiety agents, phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors, and the 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 therapy with clonazepam.

Clonazepam and it metabolites are excreted by the kidneys; to avoid excessive accumulation, caution should be exercised in the administration of 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.

ADVERSE REACTIONS

The most frequently occurring adverse reactions of clonazepam are referable to CNS depression. Studies to date have shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. However in most cases these effects are transitory and appear during the first few weeks of treatment. Behaviour problems have been noted in approximately 25% of patients and increased salivation in 7%.

Others, listed by system, are:

Central Nervous System:

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 central nervous system 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 and heptomegaly.

Genitourinary:

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

Integumentary:

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

Musculoskeletal:
Muscle weakness and low back pain.

Respiratory:
Hypersecretion in the upper respiratory passages, rhinorrhea, dyspnea and respiratory depression.
Hematopoietic:
Anemia, leukopenia (WBC below 4000/cu mm), thrombocytopenia and eosinophilia.

Liver Function:
Slight, transient elevations of transaminase and alkaline phosphatase.

Miscellaneous:
Palpitations, coated tongue, dehydration, fever, Iymphadenopathy, weight gain or loss, changes in libido, gynecomastia, hallucinations, dysdiadochokinesis, coma, and aphonia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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:

No specific antidote is known. Gastric lavage may be beneficial if performed soon after ingestion of clonazepam. Supportive measures should be instituted as indicated: maintenance of an adequate airway, intravenous fluids and monitoring of pulse, blood pressure and respiration. If necessary, a CNS stimulant, such as caffeine and sodium benzoate or methylphenidate, may be administered with caution. Levarterenol bitartrate or metaraminol bitartrate may be given for hypotension. Dialysis appears to be of no value.

DOSAGE AND ADMINISTRATION

Dosage of Zym-CLONAZEPAM is essentially individual and depends above all on the age of the patient. Dosage must be determined in each patient according to clinical response and tolerance.

Children:

In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day and should not exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.50 mg every third day until a maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the larger dose should be given before retiring.

Adults:

The initial dose for adults should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every three days until seizures are adequately controlled or until side effects preclude any further increases. Maintenance dosage must be individualized for each patient depending upon response. A recommended maintenance dose for adults is 8 to 10 mg/day in 3 divided doses.

Dosage 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 Zym-CLONAZEPAM is added to an already existing anticonvulsant regimen.

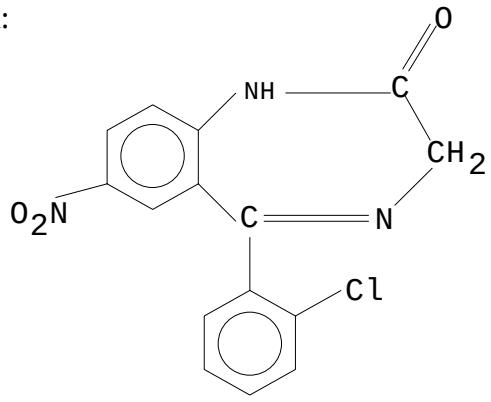
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: clonazepam

Chemical Name: 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-l, 4-benzodiazepin-2-one.

Structural Formula:



Molecular Weight: 315.7

DESCRIPTION:

Light yellow powder, having a faint odor. Melts at about 239˚. Insoluble in water; sparingly soluble in acetone and in chloroform; slightly soluble in alcohol and in ether.

COMPOSITION:

Non-Medicinal Ingredients:

Each 0.25 mg tablet contains: Lactose, Microcrystalline Cellulose, Starch, Magnesium Stearate and FD&C blue #1 lake.

Each 0.5 mg tablet contains: Lactose, Microcrystalline Cellulose, Starch, Magnesium Stearate and FD&C yellow #6 Lake.

Each 1 mg tablet contains: Lactose, Microcrystalline Cellulose, Starch, Magnesium Stearate and FD&C Red # 40 Lake.

Each 2 mg tablet contains: Lactose, Microcrystalline Cellulose, Starch and Magnesium Stearate.

STABILITY AND STORAGE RECOMMENDATIONS:

Store at 15˚ - 30˚C. Keep in tightly closed, light resistant containers.

AVAILABILITY OF DOSAGE FORMS:

0.25 mg: Each cylindrical biconvex, blue tablet imprinted “CLONAZEPAM” on one side and plain on the other side contains 250 µg clonazepam. Tablets contain lactose and are tartrazine and sodium free. Available in bottles of 100.

0.5 mg: Each orange, scored, cylindrical, biplane bevel-edged tablet is imprinted “CLONAZEPAM” on one side, scored and imprinted “R 0.5" on the other side. Tablets contain lactose and are tartrazine and sodium free. Available in bottles of 100, 500, and 1000.

1.0 mg*:* Round, standard concave tablet imprinted “CLONAZEPAM” on one side & “pms” over “1.0" on the other side. Coloured pink. Tablets are tartrazine and sodium free. Bottles of 100, 500 and 1000.

2.0 mg: Cyclindrical, biplane bevel edged tablet imprinted “CLONAZEPAM” on one side, scored and imprinted “R2.0" on the other side. Coloured white. Tablets are tartrazine and sodium free. Available in bottles of 100, 500 and 1000.

PHARMACOLOGY

Pharmacodynamics

Animal studies:

The basic anticonvulsant properties of clonazepam are similar to those of other diazepines. The following table gives an indication of the relative potency of clonazepam and other anticonvulsants in various experimental tests in animals:

Convulsant Test Oral ED50 Values (mg/kg) in mice, rats and humans

		mice(3)			RATS(1)		
Drug	Max.Human Therapeutic Dose (mg/Kg)	Metrasol Seizures	Thiosemi-carbazide Seizures	30% Strychine Threshold	Maximum Electroshock	Amygdala-kindled gene-ralized seizures	Cortical- kind. gen. seizures
Clonazepam	0.40	0.08-0.16	0.73	2.1	8.4	0.07	0.30
Diazepam	0.43	0.8-1.4	3.4	6.2	9.0	0.34	0.63
Chlordiazepoxide	1.43	-	27.0	22.2	17.2	-	-
Phenobarbital	8.5	8.0-27.0	63	37.2	7.3	10.0	12.0
Trimethadione	25.7	300	770	-	490	-	-
DPH	7.7	-	7800	7300	8.7	66.0	44.0

Clonazepam is effective in reducing photomyoclonic responses in baboons in doses less than 0.5 mg/kg i.m. However seizures evoked by local application of benzylpenicillin or strychnine do not respond well to systemic administration of clonazepam.

In cats and monkeys clonazepam produces a decrease in the amplitude of local evoked potentials from normal and secondary epileptogenic limbic tissues and suppression of the spread of primary epileptiform activity generated by an irritant focus. Other CNS effects noted in several species at varying doses include taming, disinhibitory, sedative, ataxic and hypnotic effects.

In mice clonazepam increases serotonin concentrations at synaptic junctions by decreasing its utilization and decreasing the egress of its metabolite 5-HIAA.

Blood pressure in dogs is lowered and vascular responses to serotonin and noradrenaline are inhibited by clonazepam in doses between 1 and 4 mg/kg i.v.. There is a slight myocardial depressant action at these doses. Other pharmacological effects occur only at higher doses in which gross CNS depressant effects are observed.

Human studies:

Long-term oral administration of clonazepam suppresses various forms of EEG abnormalities including: 3 cycles per second spike waves, slow spike waves, generalized spike waves and hyperarrhythmia. Generalized EEG abnormalities are more readily suppressed by clonazepam than are focal EEG abnormalities, such as focal spike.

Pharmacokinetics and metabolism

Metabolic pathways are similar in several species and the chief metabolites, 7-amino and 7-acetyl amino derivatives, have been isolated in urine of rats, dogs and humans. Hydroxylation also occurs as a prominent metabolic pathway. Metabolites are excreted primarily in urine; approximately 50% of an oral dose is excreted within 7 days and 9.1 to 30% in the feces. The excretion of the drug plus metabolites increases as the dose increases. Following single oral doses of 1.5 to 9.0 mg in
healthy and epileptic subjects, plasma levels of clonazepam were reached in 1 to 10 hours and varied between 8 to 52 ng/ml.

Doses of clonazepam are directly proportional to plasma levels and elimination follows first-order kinetics. There is no resultant accumulation of clonazepam following chronic dose administration of 1.5

to 4 mg daily and elimination half-lives vary between 22 and 33 hours.

Due to the wide interindividual variation in plasma levels neither the therapeutic effect of clonazepam nor its side effects are related to plasma levels.

TOXICOLOGY

Acute Toxicology

The following LD50 values have been calculated for clonazepam:

Species	Dose(mg/kg) and Route		
	oral	i.p.	i.v.
Mouse	>4000	>800	2.85±0.1
Rat (adult)	>4000	-	-
Rat (neonate)	550±120	-	-
Rabbit	>2000	-	-

Signs of toxicity include decreased motor activity, ataxia, piloerection and tremors.

Chronic Toxicity

Rats were fed clonazepam in the diet for 18 months in concentrations corresponding to 5, 20 and 50 mg/kg/day. No gross drug-related toxicity was evident. Slight and transient elevations in liver function tests appeared in high dose animals corresponding to increases in liver weight, but these findings were not accompanied by histologic evidence of liver damage.

A study in dogs was conducted in which animals received clonazepam in doses of 3, 10 and 30 mg/kg/day for 12 months. Weight gain was reduced in mid- and high-dose animals compared to controls. The following significant changes in laboratory values were noted: a decrease in hemoglobin and hematocrit

values in mid- and high-dose animals, a decreased albumin/globulin ratio due to decreased albumin and increased globulins in high-dose animals, increased alkaline phosphatase and bilirubin values in high-dose animals. There was a significant increase in liver weight in high dose animals.

Teratology And Reproduction Studies:

Five reproductive experiments were conducted in rats and three in rabbits with doses of clonazepam varying from 1 to 100 mg/kg/day in the former and 0.2 to 10 mg/kg/day in the latter species. The drug was administered for various periods of time prior to, during and/or after gestation in the various investigations.

In a two-litter study in rats, conception and offspring survival were reduced, possibly because of excessive tranquilization. Five offspring in one litter, whose parents had received 100 mg/kg/day, were born with various degrees of clubbing and webbing of the hind paws.

Similar anomalies also were seen in two rabbit studies. Seven of eight fetuses in one litter, whose dam had received 10 mg/kg/day between gestation days 7 to 18, had shortened fore and/or hind legs with syndactyly.

In a repeat experiment, three of ten fetuses in onelitter and ten of ten in another litter, whose dams had received 0.2 or 5 mg/kg/day respectively between gestation days 7 to 18, had similar hind leg lesions; nine of the former fetuses and ten of the latter also had cleft palates. None of the fetuses whose dams had received 1 or 10 mg/kg/day during this period had similar anomalies. The incidences of cleft palate usually are considerably lower in these rabbits.

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