# PRODUCT MONOGRAPH

## RIVOTRIL®

(clonazepam)

0.5 mg and 2 mg Tablets

Anticonvulsant

Hoffmann-La Roche Limited
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CDS Version 4.0

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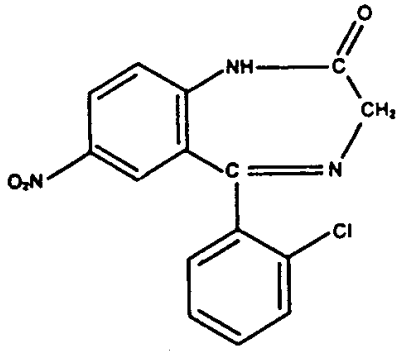
# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

| | |
|---|---|
| Proper Name: | clonazepam |
| Chemical Name: | 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-1, 4-benzodiazepin-2-one. |
| Molecular Formula: | $C_{15}H_{10}ClN_3O_3$ |
| Molecular Mass: | 315.7 |
| Structural Formula: |  |
| Physiochemical properties: | Clonazepam is a white to yellow-white odourless fine powder. The pH of clonazepam is between 5.0 and 7.0 in 1% aqueous suspension. |
| Composition: | Each tablet contains either 0.5 mg or 2.0 mg clonazepam. The non-medicinal ingredients are as follows:<br><br>**0.5 mg tablets:** cornstarch, iron oxide red, iron oxide yellow, lactose, magnesium stearate, potato starch and talc.<br><br>**2.0 mg tablets:** cornstarch, lactose, magnesium stearate and microcrystalline cellulose. |

## DETAILED PHARMACOLOGY

The pharmacological profile of clonazepam is the same as that of other anxiolytic sedative benzodiazepines. Its basic anticonvulsive properties are also similar to those of other diazepines.

**Relative Potency of Clonazepam and Other Anticonvulsants (Experimental Tests)**
The following table gives an indication of the relative potency of clonazepam and other anticonvulsants in various experimental tests in animals.

**Convulsant Test Oral $ED_{50}$ Values (mg/kg) in Mice and Humans**

| Drug | Max. Human Therapeutic Dose (mg/kg) | Metrazol Seizures | Thiosemi-carbazide Seizures | 30% Strychine Threshold | Maximum Electroshock |
|---|---|---|---|---|---|
| Clonazepam | 0.40 | 0.08 - 0.16 | 0.73 | 2.1 | 8.4 |
| Diazepam | 0.43 | 0.8 - 1.4 | 3.4 | 6.2 | 9.0 |
| Chlordiazepoxide | 1.43 | - | 27.0 | 22.2 | 17.2 |
| Phenobarbital | 8.5 | 8.0 - 27.0 | 63 | 37.2 | 7.3 |
| Trimethadione | 25.7 | 300 | 770 | - | 490 |
| DPH | 7.7 | - | 7800 | 7300 | 8.7 |

Clonazepam is effective in reducing photomyoclonic responses in baboons in doses under 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. Other CNS effects noted in several species at varying doses include taming, disinhibitory, sedative, ataxic, and hypnotic effects.

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 pharmacologic effects occur only at higher doses in which gross CNS depressant effects are observed.

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 seven days. Excretion of the drug plus metabolites increases as the dose increases.

## TOXICOLOGY

**Acute Toxicity**:

The following $LD_{50}$ values have been calculated for clonazepam:

| | Dose (mg/kg) and Route | | |
|---|---|---|---|
| **Species** | **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 weights, 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.

**Carcinogenicity:** No 2-year carcinogenicity studies have been conducted with clonazepam. However, in an 18-month chronic study in rats no treatment-related histopathological changes were seen up to the highest tested dose of 300 mg/kg/day.

**Mutagenicity:** Genotoxicity tests using bacterial systems with *in vitro* or host mediated metabolic activation did not indicate a genotoxic liability for clonazepam.

**Impairment of Fertility:** Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and impaired pup survival at doses of 10 and 100 mg/kg/day.

**Teratogenicity:** No adverse maternal or embryo-fetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively.

In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed.

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