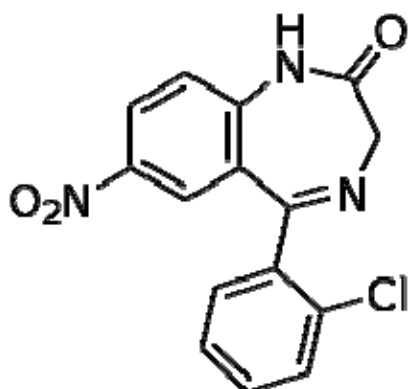


## NAME OF THE MEDICINE

### RIVOTRIL®

(clonazepam)

CAS Registry Number: 1622-61-3



## DESCRIPTION

RIVOTRIL contains an active substance, clonazepam, chemically described as 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4 benzodiazepin-2-one. It is a light yellow powder, practically insoluble in water and of molecular weight 315.7.

RIVOTRIL 0.5 mg tablets each contain 0.5 mg clonazepam and the following excipients: lactose, maize starch, potato starch, talc, magnesium stearate, iron oxide red, iron oxide yellow.

RIVOTRIL 2.0 mg tablets each contain 2.0 mg clonazepam and the following excipients: lactose, pregelatinised starch, microcrystalline cellulose, magnesium stearate.

RIVOTRIL oral liquid contains 2.5 mg/mL clonazepam (one drop contains 0.1 mg clonazepam) and the following excipients: peach flavouring 85502, saccharin sodium, glacial acetic acid, propylene glycol.

RIVOTRIL ampoules (1 mL) each contain 1 mg clonazepam and the following excipients: absolute ethanol, 30 mg benzyl alcohol, propylene glycol, glacial acetic acid; Diluent: sterile water for injection.

## PHARMACOLOGY

### Actions

Clonazepam is an anticonvulsant which exhibits several pharmacological properties characteristic of the benzodiazepine class of medicines.

The exact site and mode of action of the anticonvulsant action of clonazepam is unknown.

Benzodiazepines enhance the polysynaptic inhibitory processes at all levels of the central nervous system. Clonazepam is more effective in blocking spread of electrical activity in the lesion itself.

### Pharmacokinetics

### **Absorption and Bioavailability**

Clonazepam is rapidly and almost completely (82 – 98%) absorbed after oral administration of RIVOTRIL tablets, with peak serum levels being reached between 2 – 3 h. The absorption half-life is 24 min. RIVOTRIL tablets are similar to an oral solution with respect to the extent of clonazepam absorption, whereas the rate of absorption is different (slightly slower for the tablets). With continuous therapy accumulation occurs and although values differ in different reports, the therapeutic serum level appears to be between 10 and 80 nanogram/mL. In one study with increase in dosage to 5 mg/day the average level of clonazepam after 15 days was 54 nanogram/mL. A steady state is usually reached within 2 – 3 weeks.

Plasma concentrations of clonazepam at steady states for once daily dosage regimens are 3-fold higher than those after single oral doses. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam ranged from 30 – 80 nanogram/mL. The plasma concentration-dose relationship of clonazepam is linear.

The absolute bioavailability is 90%.

### **Distribution.**

Clonazepam enters the cerebral tissues rapidly.

The distribution half-life is approximately between 0.5 – 1 h. The apparent volume of distribution, 3 L/kg, suggests concentration in some tissues.

The plasma protein binding of clonazepam ranges from 82 – 86%.

### **Metabolism**

Clonazepam is metabolised in the liver. The metabolic pathways include hydroxylation, reduction of the nitro groups to an amine and addition of acetate to the amino grouping. Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamido-clonazepam. Hydroxylation at the C-3 position also occurs. Hepatic cytochrome P-450 3A4 is implicated in the nitroreduction of clonazepam to pharmacologically inactive metabolites.

### **Elimination**

The mean elimination half-life is  $39.0 \pm 8.3$  h. The mean clearance  $\pm$  SD is  $55.1 \pm 8.2$  mL/min following a single dose of 2 mg clonazepam given IV.

50 – 70% of the dose is excreted in the urine and 10 – 30% in the faeces as metabolites. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose. The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

### **Clinical significance of pharmacokinetics**

With chronic dosing, accumulation occurs. However, there is a wide variation in therapeutic plasma levels and a correlation between adverse effects with plasma levels or the rate of increase in plasma concentration of clonazepam and its metabolites has not been established. Consequently monitoring of plasma levels, as is often done with some anticonvulsants, would be valuable.

It should be emphasised that because of the effect of clonazepam on plasma levels of other anticonvulsants administered concomitantly (and vice versa) the patient should be monitored carefully in the initial stages for clinical response and occurrence of side effects.

### **Pharmacokinetics in Special Populations**

*Renal Failure:* Renal disease does not affect the pharmacokinetics of clonazepam. However, while based on pharmacokinetic considerations, no dosage adjustment may be required, the pharmacodynamics of probable accumulated clonazepam metabolites may necessitate dosage review in these patients.

*Hepatic Failure:* The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated. However, due to the sole hepatic metabolism of clonazepam, the pharmacokinetics of clonazepam are expected to be affected on theoretical grounds.

*Elderly:* The pharmacokinetics of clonazepam in the elderly has not been established.

*Neonates:* Although the elimination half-life ( $41.9 \pm 29.8$  h) and clearance values in neonates pre-treated with phenobarbital are the same order of magnitude as those reported in non-pretreated adults, post-natal age does however affect the clearance of clonazepam under normal conditions.

## INDICATIONS

**Tablets.** Most types of epilepsy in infants and children, especially absences (petit mal), myoclonic seizures and tonic-clonic fits, whether due to primary generalised epilepsy, or to secondary generalisation of partial epilepsy.

In adults all varieties of generalised epilepsy (including myoclonic, akinetic, tonic and tonic-clonic seizures), and in partial epilepsy (including psychomotor seizures).

**Injection.** Intravenous (IV) use, for status epilepticus.

**Note.** Efficacy by the intramuscular (IM) route has not been demonstrated.

## CONTRAINDICATIONS

RIVOTRIL is contraindicated in patients with a known hypersensitivity to benzodiazepines.

RIVOTRIL is contraindicated in patients with

- chronic obstructive airways disease with incipient respiratory failure
- severe hepatic insufficiency.
- dependence on drugs of abuse and CNS depressants including alcohol

## PRECAUTIONS

Following the prolonged use of RIVOTRIL at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from 4 weeks to 4 months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of RIVOTRIL (see Dependence below).

Only a small minority of patients with the common seizure types achieves a lasting remission with clonazepam. Tolerance to the anticonvulsant effect of clonazepam may occur after 4 weeks to 6 months of continuous treatment in the majority of patients leading to increased seizure frequency. Increasing the dose in

this situation is rarely worthwhile. If seizures are no longer being adequately controlled, the medicine should be discontinued and alternative treatment implemented.

### **Lactose intolerance**

Since RIVOTRIL contains lactose, patients with rare hereditary problems of galactose intolerance (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

### **Porphyria**

RIVOTRIL should be used with care in patients with porphyria because it may have a porphyrogenic effect.

### **Concomitant use of alcohol and CNS depressants**

The concomitant use of RIVOTRIL with alcohol and/or CNS depressants has the potential to increase the clinical effects of RIVOTRIL; possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression.

Since alcohol can provoke epileptic seizures irrespective of therapy and may potentiate the CNS depressant effects of clonazepam, it is imperative that patients should abstain from drinking alcohol while under treatment with RIVOTRIL. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of RIVOTRIL.

RIVOTRIL should be used with particular care in spinal or cerebellar ataxia, in the event of acute intoxication with alcohol, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic agents, antidepressants or lithium, or if the patient suffers from sleep apnoea.

As up to 70% of clonazepam metabolites are excreted via the kidneys, the pharmacodynamics of clonazepam and its metabolites might be altered.

### **Hypotension**

Although hypotension has occurred rarely, RIVOTRIL should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

### **Amnesia**

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

### **Myasthenia Gravis**

RIVOTRIL could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

### **Acute Narrow-angle Glaucoma**

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

### **Impaired Renal/Liver Function and Blood Dyscrasias**

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances patients on benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic blood counts and liver function tests are recommended.

### **Paradoxical Reactions**

Paradoxical reactions such as agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams, acute rage, stimulation or excitement may occur; should such reactions occur, RIVOTRIL should be discontinued.

### **Impaired Respiratory Function**

Caution in the use of RIVOTRIL is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension.

### **Depression, Psychosis and Schizophrenia**

RIVOTRIL is not recommended as primary therapy in patients with depression and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

### **Epilepsy**

When RIVOTRIL is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

### **Abuse**

Caution must be exercised in administering RIVOTRIL to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

### **Dependence**

The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, RIVOTRIL should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms

combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 – 4 h) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

### Effects on Fertility

Dietary administration of clonazepam to male and female rats was associated with a reduced pregnancy rate and impaired pup survival at doses of 60 mg/m<sup>2</sup>/day or greater (4-fold the maximal recommended human dose [MRHD]); the no-effect dose was 6 mg/m<sup>2</sup>/day (less than clinical exposure).

### Use in Pregnancy - Category B3

The risk of a mother with epilepsy giving birth to a baby with an abnormality is about THREE times that of the normal population. Some of this risk is due to the anticonvulsant medicines taken. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine.

Overall the risk of having an abnormal child is far outweighed by the dangers to the mother and foetus of uncontrolled convulsions. It is therefore recommended that:

- Women on anticonvulsant medicines receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;
- Anticonvulsant should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose;
- Folic acid supplement (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Clonazepam is a benzodiazepine. These medicines cross the placenta and appear in the foetus and may after continuous administration during a large part of pregnancy, give rise to hypotonia, reduced respiratory function and hypothermia in the newborn child. Withdrawal symptoms in newborn infants have occasionally been reported with this class of medicines.

Oral administration of clonazepam during the period of organogenesis has elicited a low, non-dose-related incidence of a similar pattern of malformations in rabbits (cleft palate, open eyelids, fused sternbrae, limb defects) and mice (exencephaly, central nervous system defects) at doses less than MRHD. These effects were not observed in rats at oral doses more than 20-fold MRHD. The clinical significance of these findings is unknown.

### Use in Lactation

RIVOTRIL must not be given to nursing women. RIVOTRIL is excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant. If there is a compelling reason for use, breast feeding should be discontinued.

### Paediatric and Neonatal Use

Salivary and bronchial hypersecretion can occur in infants and small children and supervision is required to ensure that airways remain free, especially on commencing therapy or in the event of respiratory infection. The benzyl alcohol contained in RIVOTRIL ampoules may lead to irreversible damage in the newborn, especially in the premature. Therefore, for these patients, the ampoules should only be used if no therapeutic alternative is available.

### Use in Elderly or Debilitated Patients

An increased risk of falls and fractures has been recorded in elderly benzodiazepine users.

Elderly or debilitated patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the risk of a fall.

Elderly patients, patients with pre-existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidney disease, or those who are receiving treatment with other centrally acting medications or anticonvulsant agents, require very careful dosage adjustment.

### **Carcinogenicity**

No 2-year carcinogenicity studies have been conducted with clonazepam. An 18-month chronic study in rats showed no treatment-related histopathological changes at dietary doses up to 1800 mg/m<sup>2</sup>/day (greater than 100-fold MRHD).

### **Genotoxicity**

Clonazepam and five of its metabolites were negative in bacterial gene mutation assays. Chromosomal damage assays have not been conducted with clonazepam,

### **Interaction with Other Medicines**

RIVOTRIL can be administered concurrently with one or more other anti-epileptic medicines, in which case the dosage of each medicine must be adjusted to achieve the optimum effect. Interactions have been reported between some benzodiazepines and other anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together and that serum level monitoring of the other anticonvulsant is performed more frequently.

#### *Pharmacokinetic Interactions*

The anti-epileptic medicines phenytoin, phenobarbitone, carbamazepine, and valproate may increase the clearance of clonazepam, thereby decreasing the plasma concentrations of the latter during combined treatment.

Phenytoin - the effect of clonazepam on phenytoin plasma levels is not clear as the latter may increase or decrease according to study reports.

Carbamazepine - levels may be lowered by clonazepam.

Clonazepam itself does not appear to induce the enzymes responsible for its own metabolism.

The selective serotonin reuptake inhibitors (SSRIs) sertraline and fluoxetine do not significantly affect the pharmacokinetics of clonazepam when administered concomitantly.

#### *Pharmacodynamic Interactions*

The benzodiazepines, including RIVOTRIL, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. other anticonvulsant (anti-epileptic) agents, lithium, barbiturates, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics. This is especially true in the presence of alcohol (see earlier section of PRECAUTIONS).

RIVOTRIL undergoes oxidative metabolism and, consequently, may interact with disulfiram or cimetidine resulting in increased plasma levels of RIVOTRIL. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

The anticholinergic effects of atropine and similar medicines, antihistamines and antidepressants may be potentiated.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.

Some specific interactions noted with clonazepam are:

Alcohol - epileptic patients should not under any circumstances consume alcohol while being treated with RIVOTRIL, since alcohol may alter the effect of the medicine, reduce the efficacy of treatment or produce unexpected side effects (see earlier section of PRECAUTIONS).

Sodium valproate - reports of sodium valproate causing petit mal status epilepticus with clonazepam exist.

### **Ability to Drive and Use Machines**

As with all patients taking CNS-depressant medications, patients receiving RIVOTRIL should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from RIVOTRIL therapy. Abilities may be impaired on the day following use.

## **ADVERSE EFFECTS**

Adverse effects to RIVOTRIL occur in about 50% of patients, depending on dose and are usually referable to its sedative and muscle relaxant effects and are also usually transitory. (However, they can continue in up to 10% of patients and may result in withdrawal of the medicine). Adverse effects can, to a certain extent, be avoided by a low initial dose, which is gradually increased in the absence of side effects.

*Cardiac Disorders:* Cardiac failure including cardiac arrest has been reported.

*Endocrine Disorders:* Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported.

In rare cases loss of libido may occur.

*Eye Disorders:* Particularly in long-term or high-dose treatment, reversible disorders of vision (diplopia) may occur.

*Gastrointestinal Disorders:* Hypersalivation occurs relatively commonly. The following effects have been reported in rare cases: nausea and epigastric symptoms (discomfort).

*General Disorders and Administration Site Conditions:* Fatigue (tiredness, lassitude) occurs relatively frequently and is usually transient and generally disappears spontaneously during the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.

Fever may occur.

In rare cases chest pain or headache may occur.

Paradoxical reactions including irritability have been observed (see also *Psychiatric Disorders*).

If the rate of injection is too rapid or if the vein is of insufficient calibre, there is a risk of thrombophlebitis, which may be followed by thrombosis.

*Haemic and Lymphatic System Disorders:* In rare cases thrombocytopenia may occur.

*Immune System Disorders:* Allergic reactions and very few cases of anaphylaxis have been reported to occur with benzodiazepines.

*Musculoskeletal and Connective Tissue Disorders:* Muscle weakness occurs relatively frequently, is usually transient and generally disappears spontaneously during the course of the treatment or on reduction of the dosage. It can be partially prevented by increasing the dose slowly at the start of treatment.

*Nervous System Disorders:* Drowsiness, somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia. These undesirable effects occur relatively frequently, are usually transient and generally disappear spontaneously during the course of the treatment or on reduction of the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

Vertigo occurs relatively commonly.

Particularly when treatment is over prolonged periods or at high doses, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of gait and movements (ataxia) or nystagmus may occur.

Anterograde amnesia may occur with the use of benzodiazepines at therapeutic dosages; the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible.

*Psychiatric Disorders:* Impaired concentration, restlessness, confusional state and disorientation have been observed.

Depression may occur in patients treated with RIVOTRIL, but it may be also associated with the underlying disease.

The following paradoxical reactions have been observed: excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams.

Dependence and withdrawal (see PRECAUTIONS, Dependence).

*Renal and Urinary Disorder:* In rare cases urinary incontinence may occur.

*Reproductive System and Breast Disorder:* In rare cases erectile dysfunction may occur.

*Respiratory Thoracic and Mediastinal System Disorders:* Bronchial hypersecretion occurs relatively commonly. Pharyngeal oedema has been reported in rare cases. Respiratory depression is possible, especially when clonazepam is administered IV. Depression of respiration may be increased if there is obstruction of the airways or preexisting brain damage, or if other medications, which depress respiration, have been given. This effect can be avoided by careful adjustment of the final dose.

In infants and young children, RIVOTRIL may cause increased production of saliva and bronchial secretions; therefore, special attention must be paid to maintaining patency of the airways.

*Skin and Subcutaneous Tissue Disorders:* The following effects may occur in rare cases: urticaria, pruritus, skin rash, transient hair loss (alopecia), angioneurotic oedema, pigmentation disorder.

Other adverse events which have been reported and may be related to clonazepam administration are:

*Cardiac Disorders:* palpitations, tachycardia (after IV injection);

*Endocrine Disorders:* increased libido, hirsutism;

*Gastrointestinal Disorders:* anorexia, vomiting, dyspepsia, increased appetite, constipation, dysphagia, hyperphagia, hepatomegaly;

*General Disorders and Administration Site Conditions:* ankle and facial oedema, lethargy.

*Haemic and Lymphatic System Disorders:* leucopenia, eosinophilia, anaemia, lymphadenopathy;

*Investigations:* abnormal liver function test;

*Metabolism and Nutrition Disorders:* weight gain, weight loss, dehydration;

*Nervous System Disorders:* apathy, aphonia, coma, dysdiadochokinesis (inability to perform rapid, alternating movements), hemiparesis, respiratory depression, tremor;

*Psychiatric Disorders:* dysphoria, forgetfulness, hallucinations, hysteria, insomnia, psychosis, suicidal attempt (the behavioural effects are more likely to occur in patients with a history of psychiatric disturbances);

*Renal and Urinary Disorders:* dysuria, enuresis, nocturia, urinary retention;

*Respiratory Thoracic and Mediastinal System Disorders:* chest congestion, mucus obstruction of nasopharynx, rhinorrhoea, shortness of breath.

## DOSAGE AND ADMINISTRATION

### Oral Treatment

Dosage of RIVOTRIL is essentially individualised and depends in the first instance on the age of the patient. It will be determined in each patient according to clinical response and tolerance. In order to minimise initial adverse reactions, it is essential to commence with low doses and increase the daily dose progressively until a maintenance dose suited to the individual patient has been reached. Some degree of tolerance may be observed to both the adverse and therapeutic effects. If epilepsy is not adequately controlled at the maximum recommended dosage level, alternative or combination therapy should be considered (see PRECAUTIONS).

To obtain optimum adjustment of the dose in infants and children, use of the Oral Liquid form (1 drop contains 0.1 mg clonazepam) is recommended. The ease of the divisibility of the tablets facilitates administration of low doses in adults in the early phase of treatment.

### Dosage for initiation of therapy

**Infants:** 0.3 mg/day (1 drop in the morning, 2 drops in the evening).

**Children:** 2 – 5 years: 0.5 mg/day (half a 0.5 mg tablet morning and evening);  
6 – 12 years: 0.75 mg/day (half a 0.5 mg tablet in the morning, one 0.5 mg tablet in the evening).

**Adults:** 1 mg/day (one 0.5 mg tablet morning and evening).

### Average dosage range for maintenance therapy:

Age	Daily Dose	0.5 mg Tablets	2 mg Tablets	2.5 mg/mL Oral Liquid (0.1 mg/drop) Drops
Infants (up to 2 years)	0.5 - 1 mg	1 - 2	¼ - ½	5 - 10
Small children (2 - 5 years)	1.5 - 3 mg	3 - 6	¾ - 1½	15 - 30
School children ( 6 - 12	3 - 6 mg	6 - 12	1½ - 3	30 - 60

years)				
Adults	4 - 8 mg	8 - 16	2 - 4	-

The maximum daily dose for adults is 20 mg/day.

The daily quota should, if possible, be divided into three or four doses spread over the day.

The maintenance dose should be attained after 2 to 4 weeks of treatment.

**Caution:** Do not administer drops directly into the mouth from the bottle. After each administration, ensure that the dropper is secure in the neck of the bottle. Drops should be given with a spoon. Clonazepam is compatible with water, tea or fruit juice.

### **Parenteral treatment**

Treatment of status epilepticus.

NOTE: To avoid thrombophlebitis, during IV administration a vein of sufficient calibre must be chosen and the injection must be given very slowly with continuous monitoring of respiration and blood pressure.

#### *Slow IV injection*

**Caution:** The contents of the RIVOTRIL ampoule must be thoroughly mixed with the contents of the diluent ampoule. The injection solution should be prepared immediately before use.

#### *IV infusion*

RIVOTRIL infusion mixtures prepared from 3 ampoules (3 mg) RIVOTRIL and 250 mL NaCl 0.9%, NaCl 0.45% + dextrose 2.5%, dextrose 5% or dextrose 10% can be considered physically and chemically stable for 24 h at room temperature in diffuse daylight. Do not prepare RIVOTRIL infusion with sodium bicarbonate solution as precipitation of the solution may occur.

The active ingredient, clonazepam, can be absorbed by PVC. It is therefore recommended either that glass infusion containers be used or, if PVC infusion bags are used, that the mixture be infused immediately at a rate of  $\geq 60$  mL/h.

**Infants and children:** half an ampoule (0.5 mg) by slow IV injection or infusion.

**Adults:** one ampoule (1 mg) by slow IV injection or infusion. The rate must not exceed 0.25 to 0.5 mg (0.5 to 1.0 mL of the prepared solution) per minute. This dose may be repeated as required by oral route or slow IV injection or infusion until status is controlled. A total dose of 10 mg should not be exceeded.

**Elderly:** Elderly patients are usually more sensitive to the effects of benzodiazepines. Particular care should be taken during up-titration in elderly patients. The maintenance dose will usually be in the lower range of adult dosage (see PRECAUTIONS).

**Impaired hepatic function:** The safety and efficacy of clonazepam in patients with hepatic impairment has not been studied. No data are available on the pharmacokinetics of clonazepam in hepatic disease. As clonazepam is metabolised mainly in the liver, reduced dosage may be necessary.

**Impaired renal failure:** The safety and efficacy of clonazepam in patients with renal impairment has not been studied. However, based on pharmacokinetic considerations no dose adjustment is required in these patients (see PHARMACOLOGY Pharmacokinetics in Special Populations).

## OVERDOSAGE

### *Symptoms*

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, dysarthria, nystagmus, hypotonia, hypotension, respiratory depression, coma and very rarely death. Coma may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

### *Treatment*

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 – 2 h, consider activated charcoal with airway protection if indicated.

If CNS depression is severe consider the use of flumazenil (Anexate<sup>®</sup>), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil may precipitate seizures and is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to the prescribing information for flumazenil (Anexate<sup>®</sup>), for further information on the correct use of this medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

Contact the Poisons Information Centre for advice on management of overdosage.

## PRESENTATION AND STORAGE CONDITIONS

Tablets: 0.5 mg (pale orange, scored, marked ROCHE 0,5 on reverse): 100  
2 mg (white, scored, marked ROCHE 2 on reverse): 100  
Store below 30°C

Oral Liquid: 2.5 mg/mL (clear, colourless to slightly green-yellow): 10 mL (with controlled release dropper in neck of bottle)  
Store below 25°C

Ampoules (colourless to slightly green-yellow): 1 mg/mL (with diluent): 5  
Store below 25°C

Protect from light

## **POISON SCHEDULE OF THE MEDICINE**

S4 – Prescription only medicine

## **NAME AND ADDRESS OF THE SPONSOR**

Roche Products Pty Limited  
ABN 70 000 132 865  
4 - 10 Inman Road  
Dee Why NSW 2099

Customer enquiries: 1800 233 950

**Date of TGA Approval: 28<sup>th</sup> August 2009**