AUSTRALIAN PRODUCT INFORMATION
Rivotril (clonazepam)

1. NAME OF THE MEDICINE
Clonazepam

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Rivotril tablets contain 500 micrograms clonazepam.
Rivotril oral liquid contains 2.5 mg/mL clonazepam (one drop contains 0.1 mg clonazepam).
Rivotril concentrated injection solution contains 1 mg clonazepam in 1 mL and is supplied with 1 mL diluent ampoules containing 1 mL of water for injections.

Excipients with known effect
Tablet contains sugars (as lactose)
Injection contains alcohol as 20% v/v ethanol
Oral liquid contains saccharin

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM
The tablet is a cylindrical, biplanar, pale orange tablet, marked "0,5" on upper face, and break bar on reverse face.
The oral liquid is a clear blue homogeneous liquid.
The concentrated injection solution is a clear slightly yellowish liquid. The diluent is a clear colourless liquid.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF ADMINISTRATION
Dosage
WARNING: Rivotril Oral liquid
Measure the prescribed dose of Rivotril Oral liquid as DROPS ONLY. 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. After each opening, make sure the dropper is secured within the neck of the bottle.

The dosage of Rivotril must be individually adjusted according to the patient's clinical response and tolerance. The dosage of Rivotril is essentially individualised and depends in the first instance on the age of the patient.

Before adding Rivotril to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesirable effects.

As with all antiepileptic agents, treatment with Rivotril must not be stopped abruptly, but must be reduced in a stepwise fashion (see section 4.4 Special warnings and precautions for use).

Oral Treatment
WARNING: Rivotril Oral liquid
Measure the prescribed dose of Rivotril Oral liquid as DROPS ONLY.

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 section 4.4 Special warnings and precautions for use).

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. To break the tablet, hold it with the score facing up and apply downward pressure. Rivotril tablets 0.5 mg can be divided into equal halves to facilitate dosing.

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:

Table 1: Average dosage range for maintenance therapy:

Age	**Daily Dose**	**0.5 mg Tablets**		**Oral Liquid Drops**
Infants (up to 2 years)	0.5 - 1 mg	1 tablet - 2 tablets		5 **drops** - 10 **drops**
Small children (2 - 5 years)	1.5 - 3 mg	3 tablets - 6 tablets		15 **drops** - 30 **drops**
School children (6 - 12 years)	3 - 6 mg	6 tablets - 12 tablets		30 **drops** - 60 **drops**
Adults	4 - 8 mg	8 tablets - 16 tablets		-

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.
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.

Special Populations
Elderly
Elderly patients are usually more sensitive to the effects of benzodiazepines. Particular care should be taken during up-titration in elderly patients. The lowest possible dose should be used in the elderly. The maintenance dose will usually be in the lower range of adult dosage (see section 4.4 Special warnings and precautions for use).

Impaired hepatic function
Patients with severe hepatic impairment should not be treated with clonazepam (see section 4.3 Contraindications). Patients with mild to moderate hepatic impairment should be given the lowest dose possible.

Impaired renal function
The safety and efficacy of clonazepam in patients with renal impairment has not been studied. Based on pharmacokinetic considerations no dose adjustment is required in these patients however the pharmacodynamics of probable accumulated clonazepam metabolites may necessitate dosage review in these patients (see section 5.2 Pharmacokinetic properties, Special populations).

Method of Administration
Instructions for IV Administration
Caution
The contents of the Rivotril ampoule must be thoroughly mixed with the contents of the diluent ampoule.

The solution should be prepared immediately before use.

IV injection
Note: To avoid thrombophlebitis which in turn may lead to thrombosis, during IV administration a vein of sufficient calibre must be chosen and the injection must be given very slowly with continuous monitoring of EEG, respiration and blood pressure.

IV infusion
Rivotril infusion mixtures prepared from 3 ampoules (3 mg) Rivotril and 250 mL NaCl 0.9%, NaCl 0.45% + glucose 2.5%, glucose 5% or glucose 10% can be considered physically and chemically stable for 24 hours at room temperature in diffuse daylight.

4.3 CONTRAINDICATIONS

Rivotril is contraindicated in patients with a known hypersensitivity to benzodiazepines or any of the excipients of Rivotril.

Rivotril is contraindicated in patients with

- chronic obstructive airways disease with incipient respiratory failure

- severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.

- dependence on drugs of abuse and CNS depressants including alcohol

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Some loss of effect may occur during the course of Rivotril treatment.

Use in hepatic impairment
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see section 4.3 Contraindications). Special caution should be exercised when administering Rivotril to patients with mild to moderate hepatic impairment. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic liver function tests are recommended.

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 section 4.4 Special warnings and precautions for use, Dependence).

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 that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see section 4.5 Interactions with other medicines and other forms of interactions and section 4.9 Overdose).

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 patients with ataxia, in the event of acute intoxication with alcohol or drugs, 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. The risk increases at higher doses.

Sleep apnoea
Benzodiazepines are not recommended for use in patients with sleep apnoea due to possible additive effects on respiratory depression. Sleep apnoea appears to be more common in patients with epilepsy and the relationship between sleep apnoea, seizure occurrence and post-ictal hypoxia needs to be considered in light of benzodiazepine-induced sedation and respiratory depression. Therefore, Rivotril should only be used in epileptic patients with sleep apnoea when the expected benefit exceeds the potential risk.

Myasthenia Gravis
As with any substance with CNS depressant and / or muscle relaxant properties, 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 Function and Blood Dyscrasias

Patients with impaired renal 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 are recommended.

Psychiatric and Paradoxical Reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, nervousness, hostility, anxiety, delusion, sleep disturbances, nightmares, hallucinations, psychoses, vivid dreams, acute rage, stimulation or excitement, inappropriate behaviour and other adverse behavioural effects 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 (COPD), benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. The dosage of Rivotril must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system.

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. Patients with a history of depression and/ or suicide attempts should be kept under close supervision.

Epilepsy

The dosage of Rivotril must be carefully adjusted to individual requirements in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5 Interactions with other medicines and other forms of interactions).

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. When in the judgement of the clinician, the need for dosage reduction or discontinuation arises, this should be done gradually.

IV Administration

During IV administration, a vein of sufficient calibre must be chosen and the injection administered very slowly with continuous monitoring of EEG, respiration and blood pressure. If the injection is rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis (see section 4.2 Dose and method of administration).

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 development of physical and psychological dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. The risk of dependence increases with dose and duration of treatment. It is also greater in patients with a medical history of alcohol and/or drug abuse. Abuse has been reported in poly-drug users. 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, agitation, sleep disturbances, headaches, diarrhoea, irritability, 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 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Use in the Elderly
There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Elderly or debilitated patients may be particularly susceptible to the pharmacologic effects of benzodiazepines such as giddiness, ataxia and confusion, which may increase the risk of a fall. Literature suggests that such effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug-receptor interactions, post-receptor mechanisms and organ function.

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.

Paediatric 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.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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, lamotrigine 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 depending on dosing and patient factors.

Carbamazepine - levels may be lowered by clonazepam.

Rivotril itself does not appear to induce the enzymes responsible for its own metabolism. The enzymes involved in the metabolism of Rivotril have not been clearly identified but include CYP3A4. Inhibitors of CYP3A4 (e.g., fluconazole) may impair the metabolism of Rivotril and lead to exaggerated concentrations and effects.

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

Pharmacodynamic Interactions
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 section 4.4 Special warnings and precautions for use).

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 section 4.4 Special warnings and precautions for use).

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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^2/day or greater (4-fold the maximal recommended human dose [MRHD]); the no-effect dose was 6 mg/m^2/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 sternebrae, 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.

Withdrawal symptoms in newborn infants have been reported with benzodiazepines.

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.

4.7 EFFECTS ON 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 (see section 4.5 Interactions with other medicines and other forms of interactions).

4.8 ADVERSE EFFECTS (UNDESIRABLE 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.

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.

Post-Marketing Experience

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.
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 below).

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: Impaired concentration, 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: Emotional and mood disturbances, 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: restlessness, irritability, aggressiveness, agitation, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyper activity, inappropriate behaviour and other adverse behavioural effects are known to occur. Should this occur, the use of the drug should be discontinued.

In rare cases loss and /or changes in libido may occur.

Dependence and withdrawal (see section 4.4 Special warnings and precautions for use).

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 pre-existing 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.

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Investigations: In rare cases decreased platelet count may occur.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (see

section 5.2 Pharmacokinetic properties). 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 hours, consider activated charcoal with airway protection if indicated.

If CNS depression is severe consider the use of flumazenil (Anexate®), 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®), for further information on the correct use of this medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antiepileptic agent, antipanic agent. ATC code: N03AE01

Mechanism of Action

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Clonazepam is rapidly and almost completely (82 – 98%) absorbed after oral administration of Rivotril tablets, with peak serum levels being reached between 2 – 3 hours. 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. Severe toxic effects, resulting in increased frequency of seizures for some patients, have been reported at steady state plasma concentrations above 100 ng/mL.

The absolute bioavailability is 90%.

Distribution

Clonazepam enters the cerebral tissues rapidly.

The distribution half-life is approximately between 0.5 – 1 hours. 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.

Excretion

The mean elimination half-life is 39.0 ± 8.3 hours. The mean clearance ± SD is 55.1 ± 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 Impairment

Renal impairment does not affect the pharmacokinetics of clonazepam. Therefore, based on pharmacokinetic considerations, no dosage adjustment may be required in patients with renal impairment. The pharmacodynamics of probable accumulated clonazepam metabolites may necessitate dosage review in these patients.

Hepatic Impairment: 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 Patients
The pharmacokinetics of clonazepam in the elderly has not been established.

Neonates
Although the elimination half-life (41.9 ± 29.8 hours) 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.

5.3 PRECLINICAL SAFETY DATA

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

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^2/day (greater than 100-fold MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Rivotril 0.5 mg tablets
Lactose monohydrate
Maize starch
Pregelatinised potato starch
Purified talc
Magnesium stearate
Iron oxide red
Iron oxide yellow.

Rivotril 2.5 mg/mL oral liquid
Peach flavour PHL-014725 (ARTG PI No: 108020)
Saccharin sodium
Brilliant blue FCF
Glacial acetic acid
Propylene glycol.

Rivotril 1 mg/1 mL concentrated injection solution
Absolute ethanol
Benzyl alcohol
Propylene glycol

Glacial acetic acid
Diluent: Water for injections.

6.2 INCOMPATIBILITIES

Do not prepare Rivotril infusion with sodium bicarbonate solution as precipitation of the solution may occur.

Clonazepam can be adsorbed within plastic infusion bags and infusion sets, especially those containing PVC and can lead to a reduction in clonazepam concentration by up to 50%, especially where prepared bags are stored in warm ambient conditions, or where long tubing sets or slow rates of infusion are used. If possible, PVC-containing bags and infusion sets should be avoided.

Caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets. It is recommended that alternative materials be used.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Rivotril 500 micrograms tablets
Store below 30°C. Keep tablets in original packaging to protect from light and moisture.
Rivotril 2.5 mg/mL oral liquid
Store below 25ºC.
Rivotril 1 mg/1 mL concentrated injection solution
Store below 25ºC. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Rivotril 500 micrograms tablets are supplied in PA/Al/PVC/Al blister packs of 50 tablets.
Rivotril 2.5 mg/mL oral liquid is supplied in 10 mL coloured glass Type III bottles with a child resistant HDPE closure and a controlled release LDPE dropper.
Rivotril 1 mg/1 mL concentrated injection solution is available in a pack of 5 (5 x 2 mL amber glass ampoules (containing 1 mL injection solution) and 5 x 1 mL clear glass diluent ampoules).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

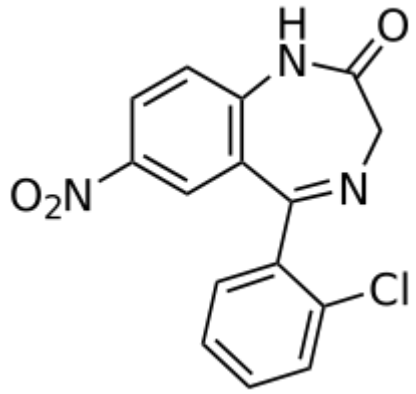
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Clonazepam is a light yellow powder which is practically insoluble in water.

Chemical structure

Clonazepam has the following chemical structure,
(5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4 benzodiazepin-2-one) and a molecular weight 315.7:



CAS number

1622-61-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8. SPONSOR

Pharmaco (Australia) Ltd
Level 13, 465 Victoria Avenue
Chatswood NSW 2067
Australia
Phone: 1800 201 564

Under license of CHEPLAPHARM Arzneimittel GmbH, Germany

9. DATE OF FIRST APPROVAL

23 August 1991

10. DATE OF REVISION

07 July 2023

Summary table of changes

Section Changed	Summary of new information
8	Transfer of sponsor