NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Rivotril® 1 mg/mL concentrated injection solution.

Antiepileptic agent

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ampoule pack: 5 ampoules containing 1 mg clonazepam in 1 mL solution plus 5 ampoules containing 1 mL sterile water for injections as diluent, to be mixed before IV or IM injection.

Excipients with known effect
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Rivotril concentrated injection solution ampoules contain a colourless to slightly green-yellow solution of 1 mg clonazepam in 1 mL solution. The diluent ampoules contain 1 mL water for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rivotril is indicated for most clinical forms of epilepsy in infants and children, in particular typical and atypical absences (Lennox-Gastaut syndrome), nodding spasms, primary or secondary generalised tonic-clonic seizures.

Rivotril may also be used in epilepsy of adults and in focal seizures.

Rivotril injection is a medicine of choice in all forms of status epilepticus.

4.2 Dose and method of administration

The dosage of Rivotril must be individually adjusted according to the patient's clinical response, tolerance of the medicine and the patient's age.

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.
An IV dose has an immediate effect which lasts for 2 - 3 hours.

Dose

<u>Parenteral Treatment</u>

Intravenous (IV) administration
The IV administration is mainly used for treatment of **status epilepticus.**

Adults
1 ampoule (1 mg) by slow IV injection or by IV infusion. This dose can be repeated as required (1 - 4 mg are usually sufficient to reverse the status). In adults, the rate of injection must not exceed 0.25 - 0.5 mg (0.5 – 1.0 mL of the prepared solution) per minute and a total dose of 10 mg should not be exceeded.

Paediatric population
Infants and children
Half an ampoule (0.5 mg) by slow IV injection or by IV infusion.

Special populations

Elderly patients
The lowest possible dose should be used in the elderly and particular care should be taken during up-titration.

Renal impairment
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 section 5.2, *Pharmacokinetics in Special Populations*).

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

Paediatric populations
See specific dosing recommendations for parenteral treatment

Method of Administration

Slow intravenous injection

The contents of the ampoule must be diluted with 1 mL of the diluent prior to administration so as to avoid local irritation of the veins. The injection solution should be prepared immediately before use. IV injection should be administered slowly with continuous monitoring of EEG, respiration and blood pressure.

Intravenous infusion

Rivotril (only the ampoule with the active substance) can be diluted for infusion (see section 6.6).

Do not prepare Rivotril infusions using sodium bicarbonate solution, as precipitation of the solution may occur (see section 6.6).

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 4.4).

Intramuscular (IM) administration

The IM route should be used only in exceptional cases or if IV administration is not feasible (after IM administration, T_{max} is 3 hours).

Special Dosage Instructions

Rivotril can be administered concurrently with one or several other antiepileptic agents, in which case the dosage of each agent must be adjusted to achieve the optimum effect**.**

As with all antiepileptic agents, treatment with Rivotril must not be stopped abruptly, but must be reduced in a stepwise fashion (see section 4.8).

Intravenous Administration

There is evidence that clonazepam can be adsorbed within plastic infusion bags and infusion sets especially those containing PVC and leading to a reduction in clonazepam concentration by up to 50%, especially where prepared bags are stored for 24 hours or more, 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 when infusing clonazepam (see section 6.6). When infusing clonazepam caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

4.3 Contraindications

Rivotril is contraindicated in patients with known hypersensitivity to clonazepam or any of the excipients listed in section 6.1 and in patients with severe respiratory insufficiency or severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.

Rivotril ampoules contain benzyl alcohol. Since there have been reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol, administration to neonates, and especially to premature infants, must be avoided.

4.4 Special warnings and precautions for use

General

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

Rivotril should be used with particular caution in patients with ataxia; in the event of acute intoxication with alcohol or drugs; and in patients with severe liver damage (e.g. cirrhosis of the liver).

Hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see section 4.3). Special caution should be exercised when administering Rivotril to patients with mild to moderate hepatic impairment.

CNS psychosis and depression

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

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

Myasthenia gravis

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Rivotril to a patient with myasthenia gravis.

Concomitant use of alcohol and/or CNS depressants

The concomitant use of Rivotril with alcohol and/or central nervous system (CNS) depressants should be avoided. Such concomitant use 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 sections 4.5 and 4.9).

Rivotril should be used with extreme caution in patients with a history of alcohol or drug abuse.

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including Rivotril, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe Rivotril concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Rivotril is used with opioids (see section 4.5).

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral effects are known to occur when using benzodiazepines (see section 4.8). Should this

occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

Amnesia

Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages.

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.

Dosage

The dosage of Rivotril must be carefully adjusted to individual requirements in patients:

- with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease);
- with pre-existing disease of the liver;
- undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5).

Anticonvulsants, including Rivotril, should not be discontinued abruptly in epileptic patients as this may precipitate status epilepticus. When, in the judgement of the clinician, the need for dosage reduction or discontinuation arises, this should be done gradually.

Like all medicines of this type, Rivotril may, depending on dosage, administration and individual susceptibility, modify the patient's reactions (e.g. driving ability, behaviour in traffic).

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).

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Porphyria

In patients with porphyria, Rivotril should be used with care because it may have a porphyrogenic effect.

Tolerance

Tolerance to benzodiazepines may develop from continued therapy. There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Drug Abuse and Dependence

Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment and is particularly pronounced in patients with a history of alcoholism and/or drug abuse, or in patients with marked personality disorders. Regular monitoring in such patients is essential.

Abuse has been reported in poly-drug abusers. Rivotril should be used with extreme caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use. Repeat prescriptions should not be given without medical review.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment or rapid dosage reduction will be accompanied by withdrawal symptoms. The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency. Withdrawal symptoms may occur with abrupt cessation of benzodiazepines following normal therapeutic doses given for short periods of time. During long-term treatment, withdrawal symptoms may develop after a lengthy period of use, especially with high doses or if the daily dose is reduced rapidly or abruptly discontinued. The symptoms include tremor, sweating, agitation, sleep disturbances and anxiety, headaches, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, mood changes, confusion, irritability and epileptic seizures which may be associated with the underlying disease. In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, hallucinations, numbness and tingling of the extremities and hypersensitivity to light, noise and physical contact. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of Rivotril should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose.

More serious manifestations of withdrawal are more common in patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Patients should be advised to consult their physician before either increasing the dose or abruptly discontinuing the medication.

A sudden discontinuation of benzodiazepines may result in convulsion. Particular care should be taken in patients with epilepsy, and other patients who have had a history of seizures, alcohol or drug dependence.

Rebound phenomenon have been described in the context of Benzodiazepine use. In some cases, patients taking Benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

Paediatric Population

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.

Elderly

Benzodiazepine pharmacologic 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.

4.5 Interaction with other medicines and other forms of interaction

Rivotril can be administered concurrently with one or more antiepileptic agents. The probability of pharmacokinetic interactions with these other medicines is low. Nevertheless, adding an extra medicine to the patient's regimen should involve a careful evaluation of the response to the treatment because unwanted effects, such as sedation and apathy are more likely to occur. In such cases, the dosage of each medicine must be adjusted to achieve the optimum desired effect.

The combination of Rivotril with valproic acid may occasionally cause petit mal status epilepticus.

Effects of other medicines on Rivotril

The antiepileptic medicines phenytoin, phenobarbital, carbamazepine, lamotrigine and to a lesser extent valproate may increase the clearance of clonazepam, thereby decreasing the plasma concentrations of the latter by up to 38% during combined treatment.

Rivotril itself does not 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 (weak CYP3A4 inducer), fluoxetine (CYP2D6 inhibitor), and the anti-epileptic drug felbmate (CYP2C19) do not affect the pharmacokinetics of clonazepam when administered concomitantly.
Rivotril has the potential to influence concentrations of phenytoin. Due to the bi-directional nature of the clonazepam-phenytoin interaction, phenytoin levels have been found to be unchanged, increased or decreased upon coadministration with Rivotril depending on dosing and patient factors.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when Rivotril is co-administered with any centrally acting depressants including alcohol.

Alcohol should be avoided in patients receiving Rivotril (see section 4.4 *Concomitant use of alcohol and/or CNS depressants*).

See sections 4.4 and 4.9 for warning of other CNS depressants, including alcohol.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. The potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

In combination therapy with centrally-acting medications, the dosage of each medicine must be adjusted to achieve the optimum effect.

4.6 Fertility, pregnancy and lactation

Pregnancy – Category B3

From preclinical studies it cannot be excluded that clonazepam might cause congenital malformations. From epidemiological evaluations there is evidence that anticonvulsants act as teratogens. However, it is difficult to determine from published epidemiological reports which medicine or combination of medicines is responsible for defects in the newborn. The possibility also exists that other factors e.g. genetic factors or the epileptic condition itself may be more important than the medication in leading to birth defects. Under these circumstances, Rivotril should only be administered to pregnant women if the potential benefits outweigh the risk to the foetus.

During pregnancy, Rivotril may be administered only if there is a compelling indication. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heartbeat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy.

Withdrawal symptoms in newborn infants have occasionally been reported with benzodiazepines.

Breastfeeding

Although the active ingredient of Rivotril has been found to pass into the maternal milk in small amounts only, mothers undergoing treatment with Rivotril should not breastfeed. If there is a compelling indication for Rivotril, breastfeeding should be discontinued.

Fertility

Preclinical studies showed a reduced pregnancy rate and impaired pup survival (see section 5.3).

4.7 Effects on ability to drive and use machines

Even if taken as directed, Rivotril can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is impaired. This effect is aggravated by consumption of alcohol.

Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. The decision on this question rests with the patient's physician and should be based on the patient's response to treatment and the dosage involved (see section 4.4).

4.8 Undesirable effects

Post-Marketing

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

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

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, behaviour, agitation, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur.
Should this occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

In rare cases, changes in libido may occur.
Dependence and withdrawal (see section 4.4, *Drug Abuse and Dependence*).

Nervous System Disorders: Impaired concentration, somnolence, muscular hypotonia, dizziness, light-headedness, ataxia and slowed reaction occur relatively frequently. These effects are usually transient and generally disappear spontaneously in 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. Headache may occur in rare cases.

Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced co-ordination of movements and gait (ataxia) and nystagmus may occur.

Anterograde amnesia may occur with 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.

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

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

Respiratory Thoracic and Mediastinal System Disorders: Respiratory depression may occur, particularly with IV administration of clonazepam. This effect may be aggravated by pre-existing airways obstruction, or brain damage, or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

In infants and young children, Rivotril may cause increased production of saliva or of bronchial secretions. Particular attention should therefore be paid to maintaining patency of the airways.

Gastrointestinal Disorders: The following effects have been reported in rare cases: nausea and epigastric symptoms.

Skin and Subcutaneous Tissue Disorders: The following effects may occur in rare cases: urticaria, pruritus, rash, transient hair loss, pigmentation changes.

Musculoskeletal and Connective Tissue Disorders: Muscle weakness occurs relatively frequently, is usually transient and generally disappears spontaneously in 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.

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

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

General Disorders and Administration Site Conditions: Fatigue (tiredness, lassitude) occurs relatively frequently, is usually transient and generally disappears spontaneously in 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.

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

If the injection is rapid or the calibre of the vein insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

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 (thrombocytopenia) may occur.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Rivotril is seldom life-threatening if the medicine is taken alone, but may lead to areflexia, apnoea, hypotension, cardio-respiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Increased frequency of seizures may occur in patients at supra-therapeutic plasma concentrations (see section 5.2). Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other CNS depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardio-respiratory effects or central nervous system effects.

Further absorption should be prevented using an appropriate method e.g. treatment within 1 - 2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion, gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe, consider the use of flumazenil, 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 is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil for further information on the correct use of this medicine.

Warning
The benzodiazepine antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N03AE01

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects.

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

There are also animal data showing in addition an effect of clonazepam on serotonin. Animal data and electroencephalographic (EEG) investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absence seizures (petit mal), slow spike wave, generalised spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

Generalised EEG abnormalities are more regularly suppressed than focal abnormalities. According to these findings clonazepam has beneficial effects in generalised and focal epilepsies.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is quickly and almost completely absorbed after oral administration of Rivotril. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. The absorption half-life is around 25 minutes. The absolute bioavailability is around 90% with large differences between individuals.

Plasma concentrations of clonazepam at steady state for a once-daily dosage regimen are 3-fold higher than those after a single oral dose; the predicted accumulation ratios for two times and three times daily regimens are 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam averaged 55 ng/mL.

The plasma concentration-dose relationship of clonazepam is linear.

After IM administration, the T_{max} is approximately 3 hours and the bioavailability is 93%. Irregularities in the absorption profiles of clonazepam after IM administration are occasionally observed.

The plasma concentrations of clonazepam, which achieve the optimum effect are between 20 and 70 ng/mL (average 55 ng/mL). Severe toxic effects including increased frequency of seizures developed in the majority of patients with steady state plasma concentrations above 100 ng/ml.

Distribution

Clonazepam distributes very rapidly to various organs and body tissues with preferential uptake by brain structures.

The distribution half-life is approximately 0.5 – 1.0 hours. The volume of distribution of clonazepam is estimated at about 3 L/kg. The plasma protein binding of clonazepam is approximately 85%. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Biotransformation

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 or weakly active metabolites.

The metabolites are present in urine both as free and conjugated (glucuronide and sulphate) compounds.

Elimination

The mean elimination half-life is 30 - 40 hours and is independent of the dose. The clearance is close to 55 mL/min irrespective of gender, but weight-normalised values declined with increasing body weight.

50 - 70% of the oral dose of clonazepam is excreted in the urine and 10 - 30% in the faeces, almost exclusively in the form of free or conjugated metabolites. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose.

Pharmacokinetics in Special Populations

Renal Impairment

Renal impairment does not affect the pharmacokinetics of clonazepam. Based on pharmacokinetic criteria, no dose adjustment is required in patients with renal impairment.

Hepatic Impairment

Plasma protein binding of clonazepam in cirrhotic patients is significantly different from that in healthy subjects (free fraction 17.1±1.0% vs 13.9±0.2%).

Although the influence of hepatic impairment on clonazepam pharmacokinetics has not been further investigated, experience with another closely related nitrobenzodiazepine (nitrazepam) indicates that clearance of unbound clonazepam might be reduced in liver cirrhosis.

Elderly Patients

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

Paediatric Patients

Overall the elimination kinetics in children are similar to those observed in adults. After therapeutic doses to children (0.03-0.11 mg/kg) the serum concentrations were in the same range (13-72 ng/ml) as effective concentrations in adults.

In neonates 0.10 mg/kg doses led to concentrations between 28-117 ng/ml at the end of a short infusion, dropping to 18 – 60 ng/ml 30 minutes later; these were tolerated with no appreciable side effects. In neonates clearance values are dependent on post-natal age. Elimination half-life values in neonates are of the same magnitude as those reported for adults.

In children clearance values of 0.42 +/- 0.32 ml/min/kg (ages 2-18 years [104]) and 0.88 +/- 0.4 ml/min/kg (ages 7-12 years were reported; these values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

5.3 Preclinical safety data

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.

Genotoxicity

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-foetal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Injection Ampoules): 159 mg/mL ethanol, 30 mg/mL benzyl alcohol, ad 1.0 mL propylene glycol, q.s. glacial acetic acid.
Diluent Ampoules: sterile water for injection.

6.2 Incompatibilities

There is evidence that clonazepam can be adsorbed within plastic infusion bags and infusion sets containing PVC and leading to a reduction in clonazepam concentration by up to 50%, especially where prepared bags are stored for 24 hours or more, in warm ambient conditions, or where long tubing sets or slow rates of infusion are used. PVC-containing bags and infusion sets should be avoided when infusing clonazepam. When infusing clonazepam, caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

6.3 Shelf life

Rivotril 1 mg/mL concentrated injection solution: 4 years

6.4 Special precautions for storage

Rivotril 1 mg/mL concentrated injection solution: Store below 30°C. Keep ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

Rivotril 1 mg/mL concentrated injection solution is contained in an amber glass ampoule. Packs contain 5 ampoules of concentrated injection solution plus 5 ampules containing 1 mL sterile water for injection, to be mixed before IV or IM injection.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Rivotril (only the ampoule with the active substance) can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg) to at least 85 ml (e.g. 3 ampoules in 250 ml) to avoid precipitation: sodium chloride 0.9%; sodium chloride 0.45% + glucose 2.5%; glucose 5% and glucose 10%. These mixtures are stable for 24 hours at room temperature.

The active ingredient can be adsorbed on plastics, especially PVC. It is therefore recommended that alternative material be used or, if PVC bags are employed, that the mixture be infused immediately and usually within 4 hours. The infusion time should not exceed 8 hours (see sections 4.2 and 6.2).

Do not prepare Rivotril infusions using sodium bicarbonate solution, as precipitation of the solution may occur.

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. Unused or expired medicine should be returned to a pharmacy for disposal.

7. MEDICINE SCHEDULE

Controlled Drug (C5).

8. SPONSOR

Roche Products (New Zealand) Limited
PO Box 109113 Newmarket
Auckland 1149
NEW ZEALAND
Medical enquiries: 0800 656 464

9. DATE OF FIRST APPROVAL

13th May 1976

10. DATE OF REVISION OF THE TEXT

11 May 2022.

Summary of Changes Table

Section Changed	Summary of new information
4.4	Update to include tolerance text and additional text on misuse, abuse, addiction, dependence and withdrawal reactions
4.4 and 4.5	Additional warnings regarding concomitant use with opioids
Throughout Data Sheet	Additional modifications to more closely align with March 2017 Data Sheet Template Guidance
All sections	Update to remove Rivotril Oral solution 2.5 mg/mL presentation