

Data Sheet

Rivotril[®]

Clonazepam oral drops 2.5 mg/mL; injection 1 mg.

Antiepileptic agent

Caution: Never administer Rivotril drops directly into the mouth from the bottle.
After each opening, make sure the dropper is secured within the neck of the bottle.

Composition

Active ingredient

Clonazepam.

Drops: 2.5 mg/mL (1 drop = 0.1 mg clonazepam).

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

Drops: peach flavouring PHL-014725, saccharin sodium, glacial acetic acid, propylene glycol and **brilliant blue FCF (E133, CI42090)***.

(* with new formulation, not yet available)

Ampoules (per mL): absolute ethanol, 30 mg benzyl alcohol, propylene glycol, glacial acetic acid;
Diluent: sterile water for injection.

Appearance

Rivotril 2.5 mg/mL drops are available as a clear, **blue*** or colourless to slightly green-yellow solution.
(*new blue formulation not yet available)

Rivotril ampoules contain a colourless to slightly green-yellow solution of 1 mg clonazepam in 1 mL solution.

Properties and Effects

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. As with other benzodiazepines these effects are thought to be mediated mainly by post-synaptic GABA mediated inhibition, although there are 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.

Pharmacokinetics

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. Bioavailability is 90% after oral administration.

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).

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.

Metabolism

Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamino-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.

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. The clearance is 55 mL/min.

Within 4 - 10 days, 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.

The elimination kinetics in children are similar to those observed in adults.

Pharmacokinetics in Special Populations

Renal failure:

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

Hepatic Failure:

The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated.

Elderly:

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

Neonates:

The elimination half-life and clearance values in neonates are of the same order of magnitude as those reported for adults.

Indications

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.

Dosage and Administration

Standard Dosage

The dosage of Rivotril must be individually adjusted according to the patient's clinical response, tolerance of the medicine and the patient's age. To ensure optimum dosage adjustment, infants and children up to the age of 10 years should be given the drops. The drops can also be used for titration.

As a general rule, Rivotril is given as low-dose, single-agent therapy in new, non-therapy-resistant cases.

A single oral dose of Rivotril begins to take effect within 30 - 60 minutes and remains effective for 6 - 8 hours in children and 8 - 12 hours in adults. An IV dose has an immediate effect which lasts for 2 - 3 hours.

Oral Treatment

To avoid adverse reactions at the beginning of therapy, it is essential to start treatment with Rivotril at a low dose and increase the daily dose progressively until the maintenance dose suited to the individual patient has been reached.

The initial dose for **infants and children up to the age of 10 years** (or up to 30 kg bodyweight) is 0.01 - 0.03 mg/kg daily given in 2 - 3 divided doses. The dose should be increased by no more than 0.25 - 0.5 mg every third day until either a daily *maintenance dose* of approximately 0.1 mg/kg of bodyweight daily has been reached or seizures are controlled or undesired effects preclude further increase. The daily *maximum dose in children* is 0.2 mg/kg of bodyweight and should not be exceeded.

Rivotril drops should be given with a spoon and may be mixed with water, tea or fruit juice.

Based on established dosages for children up to 10 years (see above) and those for adults (see below) the following can be recommended for **children between 10 and 16 years**: The initial dose is 1.0 - 1.5 mg/day given in 2 - 3 divided doses. The dose may be increased by 0.25 - 0.5 mg every third day until the individual maintenance dose (usually 3 - 6 mg/day) is reached.

The *initial dose* for **adults** should not exceed 1.5 mg/day divided into 3 doses. The dose may be increased in increments of 0.5 mg every three days until either seizures are adequately controlled or undesirable effects preclude any further increase. The *maintenance dose* must be individualised for each patient depending upon response. Usually a maintenance dose of 3 - 6 mg/day is sufficient. The maximum therapeutic dose for adults is 20 mg/day and should not be exceeded.

The daily dose should be divided into 3 equal doses. If doses are not equally divided, the largest dose should be given in the evening. The maintenance dose level is best attained after 1 - 3 weeks of treatment. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

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.

Parenteral Treatment

Intravenous (IV) administration

The IV administration is mainly used for treatment of **status epilepticus**:

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

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.

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 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% or glucose 10%. These mixtures are stable for 24 hours at room temperature.

Clonazepam can be absorbed by PVC. It is therefore recommended that either glass infusion containers be used, or, if PVC infusion bags are used, that the mixture be infused immediately or within 4 hours. The infusion time should not exceed 8 hours.

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

During IV administration, a vein of sufficient calibre must be chosen and the injection administered very slowly, with continuous monitoring of 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.

Intramuscular 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 Undesirable Effects).

Elderly Patients

Particular care should be taken during up-titration in elderly patients.

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 Pharmacokinetics in Special Populations).

Hepatic Impairment

The safety and efficacy of clonazepam in patients with hepatic impairment has not been studied. No data are available on the influence of hepatic disease on clonazepam pharmacokinetics (see Precautions).

Contraindications

Rivotril must not be used in patients with known hypersensitivity to benzodiazepines or any of the medicine's excipients.

Rivotril must not be used in patients with severe respiratory insufficiency or severe hepatic insufficiency.

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.

Precautions

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

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, clinically relevant respiratory and/or cardiovascular depression (see Interactions).

Medical history of alcohol or drug abuse

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

General

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.

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 Interactions).

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).

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.

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

Porphyria

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

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.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. 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, muscle pain, extreme anxiety, tension, restlessness, 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.

Carcinogenicity

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

Mutagenicity

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

Impairment of Fertility

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

Teratogenicity

No adverse maternal or embryo-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.

Pregnancy, Nursing Mothers

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.

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.

Undesirable Effects

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: 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, aggressive behaviour, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams.

In rare cases, loss of libido may occur.

Dependence and withdrawal (see Precautions, Drug Abuse and Dependence).

Nervous System Disorders: 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: An increased risk for falls and fractures has been reported in elderly benzodiazepine users.

Investigations: In rare cases decreased platelet count (thrombocytopenia) may occur.

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 Precautions).

Interactions

Rivotril can be administered concurrently with one or more antiepileptic agents. But 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.

Pharmacokinetic Medicine-Medicine Interactions

The antiepileptic medicines phenytoin, phenobarbital, carbamazepine, and valproate may increase the clearance of clonazepam, thereby decreasing the plasma concentrations of the latter during combined treatment.

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

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

Pharmacodynamic Medicine-Medicine Interactions

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

Enhanced effects on sedation, respiration and haemodynamics may occur when Rivotril is co-administered with any centrally acting depressants including alcohol.

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

See Precautions and Overdosage sections for warning of other CNS depressants, including alcohol.

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

Overdosage

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. 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 (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 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 (Anexate[®]) for further information on the correct use of this medicine.

Warning

The benzodiazepine antagonist Anexate[®] (active ingredient: 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.

Stability

Rivotril ampoules – store at or below 30 °C, protect from light.

Rivotril drops should be stored upright. Store at or below 30 °C.

This medicine should not be used after the expiry date shown on the pack.



Medicine Classification

Controlled Drug (C5).

Packs

Drops 2.5 mg/mL (1 drop = 0.1 mg active ingredient), 1 x 10 mL bottle

Ampoule pack containing:

5 ampoules, 1 mg active ingredient in 1 mL solution; and

5 ampoules, 1 mL sterile water for injections as diluent, to be mixed before IV or IM injection

Name and Address

Roche Products (New Zealand) Limited
PO Box 12492 Penrose
AUCKLAND 1642
NEW ZEALAND

Customer enquiries: 0800 656 464

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