

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rivotril 1 mg/ml Concentrate for solution for injection or infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 1mg clonazepam in 1ml solution.

Excipients: Also contains 30mg benzyl alcohol and 159mg/ml Ethanol.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion supplied with a solvent for parenteral use.
A clear, colourless to slightly green-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Administered intravenously, Rivotril quickly controls status epilepticus in all clinical forms.

4.2 Posology and method of administration

Rivotril sterile concentrate is for intravenous administration. For the treatment of status epilepticus, the dose and rate of administration are governed by the response of the patient.

Adults

1mg (one ampoule of active substance mixed with one ampoule of solvent for parenteral use) by slow intravenous injection.

Elderly

Care should be taken with the elderly.

Children

0.5mg (equivalent to half an ampoule of active substance mixed with half an ampoule of solvent for parenteral use) by slow intravenous injection.

Special dosage instructions

Rivotril can be administered with one or several other antiepileptic agents, in which case the dosage of each drug must be adjusted to achieve 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)

Mode of administration

Rivotril must be diluted prior to administration in order to avoid irritation of the veins, see section 6.6.

Intravenous injection of Rivotril should be into a large vein of the antecubital fossa. The injection should be given slowly - in adults, the rate of injection must not exceed 0.25mg – 0.5mg (0.5 – 1.0ml of the prepared solution) per minute – and should be administered with continuous monitoring of EEG, respiration and blood pressure. This will greatly diminish the rare possibility of hypotension or apnoea occurring. Nevertheless, facilities for resuscitation should always be available. A total dose of 20mg should not be exceeded.

Rivotril sterile concentrate may be diluted when given in intravenous infusions of saline or glucose, such as are customary in the treatment of status epilepticus, see section 6.6

4.3 Contraindications

Patients with known sensitivity to benzodiazepines or any of the drug's excipients; acute pulmonary insufficiency, severe respiratory insufficiency, sleep apnoea syndrome, myasthenia gravis, severe hepatic insufficiency.

Rivotril sterile concentrate contains 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.

Rivotril must not be used in patients in a coma, or in patients known to be abusing pharmaceuticals, drugs or alcohol.

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for clonazepam.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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

Rivotril should be used with caution in patients with chronic pulmonary insufficiency, or with impairment of renal or hepatic function, and in the elderly or the debilitated. In these cases dosage should generally be reduced.

As with all other anti-epileptic drugs, treatment with Rivotril even if of short duration, must not be abruptly interrupted, but must be withdrawn by gradually reducing the dose in view of the risk of precipitating status epilepticus. In such cases a combination with other antiepileptics is indicated. This precaution must also be taken when withdrawing another drug while the patient is still receiving Rivotril therapy.

Rivotril may be used only with particular 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).

The concomitant use of Rivotril with alcohol or/and 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 cardio-vascular depression (see 4.5).

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

Rivotril sterile concentrate contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

In infants and small children Rivotril may cause increased production of saliva and bronchial secretion. 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) or liver and in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see section 4.5). Effects on the respiratory system 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.

Clonazepam is considered to be probably nonporphyrinogenic, although there is some conflicting evidence. Therefore in patients with porphyria, clonazepam should be used with care.

Like all drugs of this type, Rivotril may, depending on dosage, administration and individual susceptibility, modify the patient's reactions (e.g. driving ability, behaviour in traffic). (see 4.7)

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on Rivotril, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

During I.V. 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. Furthermore, respiratory depression can occur, particularly on i.v. administration of Rivotril.

In adults, the rate of injection must not exceed 0.25-0.5 mg (0.5-1 ml of the prepared solution) per minute (see 4.2). Undesirable nervous and muscle system effects and fatigue, which occur relatively frequently and are usually transient, 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 (see 4.8).

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products (see 4.8). In particular long-term or high-dose treatment, may lead to reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia), nystagmus and vision (diplopia). Furthermore, the risk of anterograde amnesia, which may occur using benzodiazepines at therapeutic dosages, increases at higher dosages. Amnestic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures (see 4.8) during long-term treatment is possible.

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.

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, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact or hallucinations. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should therefore be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose. The risk of withdrawal symptoms is increased when benzodiazepines are used together with day-time sedatives (crossed tolerance).

4.5 Interaction with other medicinal products and other forms of interaction

Since alcohol can provoke epileptic seizures, irrespective of therapy, patients must under no circumstances drink alcohol while under treatment with antiepileptic drugs. In combination with Rivotril, alcohol may modify the effects of the drug, compromise the success of therapy or give rise to unpredictable side-effects.

See section 4.9 Overdose for warning of other central nervous system depressants, including alcohol.

Enhanced effects on sedation, respiration and haemodynamics may occur when Rivotril is co-administered with any centrally acting depressants e.g. alcohol, and other anticonvulsant (antiepileptic) agents, anaesthetics, hypnotics, psychoactive drugs and some analgesics as well as muscle relaxants and may result in mutual potentiation of drug effects.

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

When Rivotril is used in conjunction with other anti-epileptic drugs, side-effects such as sedation and apathy and toxicity may be more evident, particularly with hydantoins or phenobarbital and combinations including them. In such cases, the dosage of each drug must be adjusted to achieve the optimum desired effect, particularly in the initial stages of treatment. The combination of Rivotril and sodium valproate has, rarely, been associated with the development of absence status epilepticus. Although some patients tolerate and benefit from this combination of drugs, this potential hazard should be borne in mind when its use is considered.

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

In concurrent treatment with phenytoin or primidone a change, usually a rise, in the serum concentration of these two substances has occasionally been observed.

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

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

Known inhibitors of hepatic enzymes, e.g. cimetidine, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, may increase the clearance of benzodiazepines.

4.6 Fertility, pregnancy and lactation

Preclinical studies in animals have shown reproductive toxicity and from preclinical studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations (see section 5.3). From epidemiological evaluations there is evidence that anticonvulsant drugs act as teratogens. However, it is difficult to determine from published epidemiological reports which drug or combination of drugs 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 drug therapy in leading to birth defects. 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. Rivotril has harmful pharmacological effects on pregnancy and the foetus/newborn child. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heart beat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed a physical dependence and may be at some risk for developing withdrawal symptoms in the post-natal period. 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 this drug should not breastfeed. If there is a compelling indication for Rivotril, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

As a general rule, epileptic patients are not allowed to drive. Even when adequately controlled on Rivotril, it should be remembered that any increase in dosage or alteration in timings of dosage may modify patients' reactions, depending on individual susceptibility. Even if taken as directed, clonazepam 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.

4.8 Undesirable effects

The following have been observed:

Immune System Disorders

Allergic reactions and very rare 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, disorientation have been observed. Depression may occur in patients treated with Rivotril, but it may be also associated with the underlying disease. The following paradoxical reactions have been observed: excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares, vivid dreams and psychotic disorders and activation of new types of seizures may be precipitated. If these occur, the benefit of continuing the drug should be weighed against the adverse effect. The addition to the regimen of another suitable drug may be necessary or, in some cases, it may be advisable to discontinue Rivotril therapy.

In rare cases loss of libido may occur.

Nervous System Disorders

Somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia and co-ordination disturbance. These undesirable effects occur relatively frequently and 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 was observed in rare cases. Causing of generalised fits was observed very rarely.

Particularly in long-term or high-dose treatment, reversible disorders such as dysarthria, reduced coordination of movements and gait disorder (ataxia) and nystagmus may occur. Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages. Amnestic 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.

Common: nystagmus

Cardiac Disorders

Cardiac failure including cardiac arrest has been reported.

Respiratory, Thoracic and Mediastinal System Disorders

Respiratory depression may occur, particularly on i.v. 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, particularly those with a degree of mental impairment, Rivotril may cause increased production of saliva or of bronchial secretion. Particular attention should therefore be paid to maintaining patency of the airways.

Gastrointestinal Disorders

The following effects have been reported in rare cases: nausea, gastrointestinal and epigastric symptoms.

Skin and Subcutaneous Tissue Disorders

The following effects may occur in rare cases: urticaria, pruritus, rash, transient hairloss, pigmentation changes and angioedema.

Musculoskeletal and Connecting Tissue Disorders

Muscle weakness, this undesirable effect occurs relatively frequently and 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), this undesirable effect occurs relatively frequently and 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). 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. In adults, the rate of injection must not exceed 0.25 – 0.5mg (0.5 – 1ml of the prepared solution) per minute (see section 4.2). 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 may occur. As with other benzodiazepines, isolated cases of blood dyscrasias and abnormal liver function tests have been reported.

Dependence and withdrawal, (see 4.4).

Although Rivotril has been given uneventfully to patients with porphyria, rarely it may induce convulsions in these patients.

Paediatric population

For paediatric specific events please refer to the information listed under headings: *Endocrine Disorders and Respiratory, Thoracic and Mediastinal System Disorders* in section 4.8.

4.9 Overdose

Symptoms

The symptoms of overdosage or intoxication vary greatly from person to person depending on age, bodyweight and individual response. Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Rivotril is seldom life-threatening if the drug is taken alone, but may lead to coma, areflexia, apnoea, hypotension and cardiorespiratory depression. 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 severe chronic obstructive airways disease.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Management

1. Maintain a clear airway and adequate ventilation if indicated.
2. Supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.
3. 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.
4. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.
5. Patients who are asymptomatic at 4 hours are unlikely to develop symptoms.
6. Flumazenil, a benzodiazepine antagonist is available but should rarely be required. If CNS depression is severe consider the use of flumazenil. 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 drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this drug. Flumazenil is **NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC TEST"**

Warning

The use of flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Although flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivative, ATC code: N03AE01

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. Animal data and electroencephalographic investigations in man have shown that clonazepam rapidly suppresses many types of paroxysmal activity including the spike and wave discharge in absences 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 readily suppressed by clonazepam than are focal EEG abnormalities such as focal spikes. Clonazepam has beneficial effects in generalised and focal epilepsies.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is quickly and completely absorbed after oral administration of Rivotril. Peak plasma concentrations are reached in most cases within 1 - 4 hours after an oral dose. Bioavailability is 90% after oral administration.

Routine monitoring of plasma concentrations of Rivotril is of unproven value since this does not appear to correlate well with either therapeutic response or side-effects.

Distribution

The mean volume of distribution of clonazepam is estimated at about 3 l/kg. Clonazepam must be assumed to cross the placental barrier and has been detected in maternal milk.

Metabolism

The biotransformation of clonazepam involves oxidative hydroxylation and reduction of the 7-nitro group by the liver with formation of 7-amino or 7-acetylamino compounds, with trace amounts of 3-hydroxy derivatives of all three compounds, and their glucuronide and sulphate conjugates. The nitro compounds are pharmacologically active, whereas the amino compounds are not.

Elimination

The elimination half-life is between 20 and 60 hours (mean 30 hours).

Within 4 - 10 days 50 - 70% of the total radioactivity of a radiolabeled 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. Less than 0.5% appears as unchanged clonazepam in the urine.

Pharmacokinetics in special clinical situations

Based on kinetic criteria no dose adjustment is required in patients with renal failure.

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 300mg/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 100mg/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 40mg/kg/day respectively.

In several rabbit studies following doses of clonazepam of up to 20mg/kg/day, a low non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused sternbrae and limb defects) was observed (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active substance ampoule:

Ethanol absolute
Glacial acetic acid
Benzyl alcohol
Propylene glycol

Solvent for parenteral use:

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened ampoules 4 years.

Shelf-life of diluted product: from a chemical and physical stability point of view, the diluted product is stable up to 12 hours. However, it should be used immediately after dilution in order to reduce the possibility of microbial contamination unless it is diluted under validated aseptic conditions. See section 6.6 for instructions on dilution.

6.4 Special precautions for storage

Do not store above 30°C. Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

5 or 10 x 2 ml amber glass ampoules each containing 1 ml active concentrate containing 1mg clonazepam.
5 or 10 x 1 ml clear glass ampoules each containing 1 ml of solvent for parenteral use.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation of intravenous injection:

The contents of the solvent ampoule, which contains 1ml Water for Injection, *must* be added to the contents of the other ampoule, which contains 1mg clonazepam in 1ml, *immediately* before injection.

Preparation of intravenous infusion:

3mg clonazepam (3 ampoules) can be diluted in 250ml of the following solutions:

Sodium Chloride Intravenous Infusion 0.9% w/v
Glucose Intravenous Infusion 5% and 10%
Sodium Chloride and Glucose Intravenous Infusion (0.45% sodium chloride and 2.5% glucose)

The active ingredient clonazepam can be absorbed on PVC. It is therefore recommended either glass containers be used or, if PVC infusion bags are used, that the mixture be infused straight away over a period of no longer than 2 hours.

Each ampoule is for single use only. Discard any unused solution after use.

7 MARKETING AUTHORISATION HOLDER

Roche Products Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

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