Rivotril®

Clonazepam

Composition

Active ingredient: clonazepam.

Excipients:

Rivotril concentrate for solution for injection (double ampoules):

Concentrate: acetic acid, ethanol, preservative: benzyl alcohol, propylene glycol.

Diluent: sterile water for injections.

Rivotril tablets (cross-scored):

Rivotril tablets contain lactose.

Rivotril oral drops:

Colour.: E-133, saccharin, flavours.

Pharmaceutical form and quantity of active substance per unit

Rivotril concentrate for solution for injection (double ampoules):

Concentrate (1 ampoule of 1 ml): 1 mg clonazepam per 1 ml.

Diluent (1 ampoule of 1 ml): water for injections.

Rivotril tablets, 0.5 mg:

Light-orange scored tablets, 0.5 mg clonazepam.

Rivotril tablets, 2 mg:

White cross-scored tablets, 2.0 mg clonazepam.

Rivotril oral drops:

Oral solution, 2.5 mg clonazepam/ml (equivalent to 25 drops; 1 drop is equivalent to 0.1 mg clonazepam).

Indications and potential uses

Most clinical forms of epilepsy in infants and children, in particular typical and atypical absences (Lennox syndrome), infantile spasms, primary or secondary generalised tonic-clonic spasms.

Rivotril i.v. or i.m. is a drug of choice in all forms of status epilepticus.

Rivotril can also be used in adult epilepsy and focal seizures.

Dosage and administration

General information

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

Rivotril 0.5 mg tablets can be halved to facilitate dosing. Rivotril 2 mg tablets can be halved or quartered to facilitate dosing. To break the tablet, hold it with the score facing up and apply downward pressure.

Before Rivotril is added to an existing anticonvulsant regimen, it should be considered that this may result in an increase in undesired effects.

Standard dosage

To ensure optimum dosage adjustment, infants should be given the drops and children the 0.5 mg tablets. The scored 0.5 mg tablets facilitate the administration of lower doses to adults in the initial stages of treatment.

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

Oral treatment

To avoid adverse effects at the beginning of treatment, it is particularly important to increase the daily dose (tablets or drops) progressively until the maintenance dose required for the individual patient has been reached.

Rivotril drops should be mixed with water, tea or fruit juice and administered with a spoon. Never administer Rivotril drops directly into the mouth. Check that the dropper is seated securely in the bottle neck on each occasion after the bottle has been opened.

Infants and children up to the age of 10 years (or up to 30 kg bodyweight)

The initial dose is 0.01–0.03 mg/kg bodyweight daily given in 2–3 divided doses. This dose may be increased by no more than 0.25–0.5 mg every three days until a daily

maintenance dose of 0.05–0.1 mg/kg bodyweight daily has been reached or seizures are controlled or undesirable effects preclude further increase.

The maximum daily dose in children should not exceed 0.2 mg/kg bodyweight.

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

Children above the age of 10 years (or over 30 kg bodyweight)

Based on the established dosages for children up to 10 years (see above) and adults (see below), the recommended initial dose is 1 to 1.5 mg/day given in 3 divided doses. The dose may be increased by 0.25–0.5 mg every three days until the individual maintenance dose of 3–6 mg/day is reached.

Adults

The initial dose should not exceed 1.5 mg/day given in 3 divided doses. This dose may be increased by 0.5 mg every three days until either seizures are adequately controlled or undesirable effects preclude an increase. The maintenance dose must be individually adjusted for each patient, depending on clinical response. Generally a maintenance dose of 4–8 mg/day is sufficient. The maximum therapeutic dose for adults is 20 mg/day and should not be exceeded.

The initial daily dose should be divided into 3 equal doses. Where a number of unequal doses are required, the largest dose should be taken in the evening. The daily maintenance dose is best reached after 1–3 weeks of treatment. Once the maintenance dose has been reached, the daily amount may be given as a single dose in the evening.

Parenteral treatment

Special dosage instructions:

The active ingredient clonazepam can be adsorbed to some extent onto plastic infusion bags and infusion sets, especially those made of PVC. This may lead 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. When infusing Rivotril caution should be exercised when switching between PVC and non-PVC-containing bags and infusion sets.

It is recommended that PVC-containing bags and infusion sets be avoided when infusing Rivotril and that glass containers be used instead or, if PVC infusion bags are used, that the mixture be infused immediately at a rate of ≥ 60 ml/h within 4 hours. The infusion time should not exceed 8 hours.

The concentrate of 1 ml containing 1 mg of active ingredient may be used only after addition of 1 ml of diluent in order to avoid local irritation of the veins. The injection syringe then contains 2 ml of ready-to-use injection solution with 1 mg of active substance (concentration: 0.5 mg/ml). The injection solution should be prepared

immediately before use. Intravenous administration should be carried out very slowly into a vein of sufficient diameter, with continuous monitoring of EEG, respiration, and blood pressure (see *Warnings and precautions*). Intra-arterial injection must be avoided with certainty because of the risk of necrosis and its consequences.

Intravenous injection/infusion for treatment of status epilepticus

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

Adults: 1 ampoule (1 mg) by slow i.v. injection or by i.v. infusion.

This dose can be repeated as required, possibly as an i.v. infusion (1–4 mg is 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 diluted solution) per minute and a total dose of 10 mg should not be exceeded (see *Warnings and precautions*).

In order to avoid precipitation, Rivotril can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg active substance ampoule) to at least 85 ml (e.g. 3 ampoules in at least 250 ml): 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.

Sodium bicarbonate solution must not be used for dilution, as precipitation may occur (see *Additional information, Incompatibilities*).

Intramuscular injection

The i.m. route should be used only in exceptional cases or if i.v. administration is not feasible (after i.m. administration t_{max} is approximately 3 hours).

Special dosage instructions

Elderly patients

Limited data are available on clinical trials of clonazepam in epileptic patients over 65 years of age.
The lowest possible dose should be used in elderly patients (see *Pharmacokinetics, Pharmacokinetics in special patient groups*), and particular care should be taken during up-titration.

Renal impairment

The safety and efficacy of clonazepam in patients with renal impairment have not been studied; based on pharmacokinetic criteria, however, no dose adjustment is required in these patients (see *Pharmacokinetics, Pharmacokinetics in special patient groups*).

Hepatic impairment

Patients with severe hepatic impairment must not be treated with Rivotril (see *Contraindications*). Patients with mild to moderate hepatic impairment should receive the lowest possible dose.

Rivotril can be administered concurrently with one or more 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; instead, the dosage must be reduced in stepwise fashion (see *Warnings and precautions* and *Undesirable effects*).

Contraindications

Rivotril must not be used in the following situations:

- known hypersensitivity to clonazepam or any excipients of the product
- severe respiratory failure
- severe hepatic impairment
- known existing drug or alcohol dependence
- myasthenia gravis.

Rivotril ampoules contain benzyl alcohol as a preservative. Since there have been reports of permanent neuropsychiatric disorders and disturbances of multiple organ systems in association with benzyl alcohol, Rivotril ampoules must not be administered to neonates, especially premature neonates.

Warnings and precautions

Warnings:

General

Some loss of efficacy may occur during treatment with clonazepam.

There may be a paradoxical increase in seizure frequency or a new type of seizures. Particularly careful individual dosing is required in patients receiving concomitant treatment with other centrally acting medications or anticonvulsants (see *Interactions*). Concomitant treatment with valproate and clonazepam may provoke absence status.

Anticonvulsants, including Rivotril, should not be discontinued abruptly, as this may precipitate status epilepticus in epileptic patients. When dose reduction or discontinuation of treatment is required, it should be effected gradually.

Clonazepam should be used with particular caution in patients with spinal or cerebellar ataxia.

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.

Hepatic impairment

Benzodiazepines may have a contributory role in precipitating hepatic encephalopathy in severe hepatic impairment. Clonazepam must therefore not be administered in severe hepatic impairment (see *Contraindications*). Particular caution is required when using Rivotril to treat patients with mild to moderate hepatic impairment, who should therefore receive the lowest possible dose.

Neonates, infants and young children

Because they contain benzyl alcohol, Rivotril ampoules must not be administered to neonates, especially premature neonates. Benzyl alcohol can cause toxic and allergic reactions in children up to 3 years of age.

Rivotril may cause increased salivation or bronchial hypersecretion, particularly in infants and young children. Therefore, special attention must be paid to maintaining patency of the airways.

Dependence

Even when administered in the therapeutic range, treatment with benzodiazepines such as clonazepam can lead to physical and psychological dependence. This risk increases with high doses, prolonged treatment and particularly in predisposed patients with a history of alcohol or drug dependence, personality disorders or other serious psychiatric disorders. Abuse has been reported in polydrug users. Rivotril should be used with extreme caution in patients with a history of alcohol or drug abuse (see *Interactions* and *Overdose*).

In the case of physical dependence, abrupt termination of treatment is accompanied by withdrawal symptoms.

Rebound phenomena/withdrawal symptoms

During long-term treatment, withdrawal symptoms may develop after prolonged use, especially with high doses or if the daily dose is reduced rapidly or the drug is abruptly discontinued. The symptoms may include restlessness, sleep disturbance and anxiety, diarrhea, extreme anxiety, tension, agitation, mood changes, confusion and irritability associated with the underlying disease. In severe cases the following symptoms may occur: derealisation, depersonalisation or hallucinations. Since the risk of withdrawal symptoms is greatest after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and treatment – even if only of short duration – should be terminated by gradually reducing the daily dose.

Concomitant use of alcohol and/or CNS depressants

Rivotril should not be taken concomitantly with alcohol and/or central nervous system (CNS) depressants. Such concomitant use has the potential to increase the clinical effects of Rivotril, possibly including deep sedation that could result in coma or death, as well as clinically relevant respiratory and/or cardiovascular depression (see *Interactions* and *Overdose*).

History of alcohol or drug abuse

Abuse of Rivotril has been reported in polydrug dependence. Rivotril must be used with extreme caution in patients with known alcohol or drug abuse.

Rivotril should be used with particular caution in the event of acute intoxication with alcohol or drugs.

Psychosis and depression

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

Patients with a depressive or suicidal history should be kept under close supervision.

Psychiatric and "paradoxical" reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines (see *Post-marketing data*). If this is the case, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and adolescents and in elderly patients. These age groups in particular require careful individual dosing.

Amnesia

Anterograde amnesia can occur when using benzodiazepines at therapeutic doses, the risk increasing at higher doses. Amnesic effects may be associated with inappropriate behaviour.

Sleep apnea

Benzodiazepines are not recommended for use in patients with sleep apnea due to possible additive effects on respiratory depression. Sleep apnea appears to be more common in epileptic patients; hence the relationship between sleep apnea, seizure onset and postictal hypoxia must be taken into account in light of the sedation and respiratory depression induced by benzodiazepines. Rivotril should therefore be used in epileptic patients with sleep apnea only if the expected benefit outweighs the potential risk.

Respiratory disorders

The dosage of Rivotril must be adjusted particularly carefully to individual requirements in patients with pre-existing disease of the respiratory system (e.g. chronic obstructive pulmonary disease). The respiratory depressant effect may be aggravated by pre-existing airway obstruction or brain damage or concomitant use of other medications that cause respiratory depression.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance (Lapp lactase deficiency or glucose-galactose malabsorption) should not take the tablets.

Porphyria

Rivotril should be used with caution in patients with porphyria because it may have a porphyrogenic effect.

Precautions for use:

Parenteral administration

A vein of sufficient diameter must be chosen for i.v. administration, and the injection administered very slowly with continuous monitoring of the EEG, respiration and blood pressure (see "Instructions for use and handling"). The injection rate in adults should not exceed 0.25 to 0.5 mg (0.5 to 1.0 ml of the ready-to-inject solution) per minute (see "Dosage and administration"). If the injection is rapid or the vein is of insufficient calibre, there is an increased risk of thrombophlebitis, which may in turn lead to thrombosis.

Oral administration

Never administer the drops directly into the mouth. Make sure that the dropper is secured within the neck of the bottle on each occasion after the bottle has been opened.

Interactions

Rivotril can be administered concurrently with one or more antiepileptic agents. When another medication is added to a patient's existing treatment, the clinical response should always be very carefully evaluated, since unwanted effects such as sedation and apathy are more likely to occur. In such cases the dosage of each drug must be adjusted to achieve the desired optimum effect.

Pharmacokinetic interactions:

Concomitant use of hepatic enzyme inducers such as barbiturates and of antiepileptic medications such as phenytoin, phenobarbital, carbamazepine, lamotrigine and to a small extent valproate may increase the clearance of clonazepam and decrease its plasma concentrations by up to 38%. Rivotril may affect the concentration of phenytoin.

Because clonazepam and phenytoin interact, the concentration of phenytoin has been found to be unchanged, increased or decreased on coadministration with Rivotril, depending on dosage and patient factors. Rivotril itself does not induce the enzymes responsible for its own metabolism. Apart from CYP3A4, the enzymes involved in the metabolism of Rivotril have not been clearly identified. Inhibitors of CYP3A4 (e.g. fluconazole) may impair the metabolism of Rivotril and lead to exaggerated concentrations and effects.

The selective serotonin reuptake inhibitors sertraline (weak CYP3A4 inducer) and fluoxetine (CYP2D6 inhibitor), and the antiepileptic drug felbamate (CYP2C19 inhibitor; CYP3A4 inducer) do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic interactions:

The combination of Rivotril with valproic acid may occasionally lead to the development of absence status epilepticus.

Increased adverse reactions such as sedation and cardiorespiratory depression are also possible when Rivotril is coadministered with CNS depressants including alcohol.

Patients receiving Rivotril should avoid alcohol (see *Warnings and precautions*).

Notes on other CNS depressants including alcohol can be found under *Warnings and precautions* and *Overdose*.

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

Pregnancy and lactation

Pregnancy

Rivotril must not be used during pregnancy unless clearly necessary. If Rivotril is prescribed for a woman of childbearing potential, she should be told to contact her doctor immediately if she wishes to become, or suspects that she is, pregnant. It should be borne in mind that both pregnancy itself and abrupt discontinuation of treatment can cause exacerbation of epilepsy.

Clonazepam crosses the placental barrier.

Animal studies have shown that Rivotril has adverse effects on the fetus (cleft palate, open eyelids, sternebral fusion and limb defects, see *Preclinical data*); however, controlled studies have not been performed in humans.

From preclinical studies it cannot be excluded that clonazepam can cause congenital malformations. There are case reports of malformations and mental retardation in prenatally exposed children following benzodiazepine overdose and intoxication. Epidemiological evaluations have shown that anticonvulsants 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 epilepsy itself, may be more important than the drug treatment in leading to birth defects.

If treatment with Rivotril is essential, it should be administered at the lowest dose necessary to control seizures. This is especially important in the first trimester of pregnancy. Combination with other anticonvulsants should be avoided if possible.
Should Rivotril administration be required at a late stage of pregnancy or during delivery for urgent reasons, then corresponding effects must be expected in the unborn child (e.g. cardiac arrhythmias) and/or in the newborn (e.g. mild respiratory failure), hypothermia, hypotonia and decreased sucking reflex, or floppy infant syndrome).
Children of mothers who have used benzodiazepines for lengthy periods during pregnancy may develop physical dependence. Withdrawal symptoms have been reported in newborn infants.

Lactation

Rivotril should not be used by breastfeeding mothers, since it enters breast milk. Where there is a compelling reason for its use, breastfeeding must be discontinued.

Effects on ability to drive and use machines

Rivotril has a pronounced effect on the ability to drive and operate machines.

Even when taken as directed, Rivotril can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is seriously 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 rests with the patient's physician and should be based on the individual dosage and the patient's response to treatment (see *Interactions* and *Undesirable effects*).

Undesirable effects

The adverse events most frequently reported for Rivotril are assignable to the system organ classes of nervous system disorders and psychiatric disorders. Drowsiness has occurred to date in approximately 50% of patients and ataxia in approximately 30%. Behavioural disturbances have been observed in approximately 25% of patients. These adverse effects are usually transient and in general spontaneously reversible in the course of treatment or on reducing the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment. If paradoxical reactions occur during treatment with Rivotril, gradual discontinuation of treatment should be considered (see *Post-marketing data*).

Dependence and withdrawal reactions may occur (see *Warnings and precautions*).

Anterograde amnesia can occur when using benzodiazepines at therapeutic dosage, the risk increasing with increasing doses. Amnesic effects may be associated with inappropriate behaviour.

Falls and fractures have been reported in patients treated with benzodiazepines. The risk is increased in those using concomitant sedatives (including alcoholic beverages) and in elderly patients.

Respiratory depression may occur, particularly with intravenous administration of Rivotril. This effect may be aggravated by airway obstruction or pre-existing brain damage and after using other medications that depress respiration, and can generally be avoided by careful adjustment of the dose to individual requirements.

Heart failure, including cardiac arrest, has been reported in patients using Rivotril.

As far as possible, undesirable effects are categorised into the following frequencies: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000) and isolated cases (frequency cannot be estimated from the available data).

The data are derived from clinical trials and post-marketing experience.

Immune system disorders

Allergic reactions; in very rare cases anaphylactic shock.

Psychiatric disorders

Emotional and mood disturbances, confusion, and disorientation have been observed.

Depression can develop during treatment with Rivotril, but may also be associated with the underlying disease.

The following paradoxical reactions have been observed: restlessness (agitation), excitability, irritability, aggressiveness, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, amnesic effects with inappropriate behaviour and other adverse behavioural effects. Paradoxical reactions are more likely to occur in children and elderly patients.

In rare cases, changes in libido and impotence may occur.

Dependence and withdrawal reactions (see *Warnings and precautions*).

Blood and lymphatic system disorders

In rare cases, thrombocytopenia.

Nervous system disorders

Drowsiness and light-headedness. Impaired concentration, fatigue, exhaustion, somnolence, slowed reaction, muscular hypotonia, dizziness and ataxia are common. Headache has occurred in rare cases.

Particularly with prolonged treatment or high doses, reversible disorders such as unsteadiness of gait and movements (ataxia), disorders of vision (double vision, nystagmus), and a slowing or slurring of speech (dysarthria) can occur.

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

Anterograde amnesia.

Eye disorders

Diplopia may occur during long-term treatment or at high dosage. This effect is reversible.

Commonly, nystagmus.

Cardiac disorders

Heart failure including cardiac arrest.

Respiratory, thoracic and mediastinal disorders

Respiratory depression, angioedema, laryngeal edema, chest pain.

Gastrointestinal disorders

In rare cases, nausea and epigastric symptoms.

Skin and subcutaneous tissue disorders

In rare cases, urticaria, pruritus, skin rash, transient hair loss and pigmentation changes.

Musculoskeletal and connective tissue disorders

Muscular hypotonia; commonly, muscle weakness. These effects are usually transient and in general spontaneously reversible in the course of treatment or on reducing the dosage. They can be partially prevented by increasing the dose slowly at the start of treatment.

Renal and urinary disorders

In rare cases, urinary incontinence.

Reproductive system and breast disorders

In rare cases, erectile dysfunction.

General disorders and administration site conditions

Withdrawal symptoms (see above *Warnings and precautions).*

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

Hypersensitivity reactions can occur due to the presence of benzyl alcohol (see *Warnings and precautions*).

Injury, poisoning and procedural complications

Falls and fractures.

Children and adolescents

Endocrine disorders

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

Psychiatric disorders

Paradoxical reactions are more likely to occur in children (and the elderly).

Respiratory, thoracic and mediastinal disorders

In infants and young children, Rivotril may cause increased salivation and overproduction of bronchial secretions. Therefore, special attention should be paid to maintaining patent airways.

Overdose

Symptoms

Benzodiazepines often cause drowsiness, unsteady movement and gait (ataxia), slowed or slurred speech (dysarthria) and nystagmus. Rivotril overdose is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Patients may experience increased seizures at supratherapeutic plasma concentrations (see *Pharmacokinetics, Absorption*). The respiratory depressant effect of benzodiazepines may exacerbate existing respiratory disorders, and this effect is therefore more serious in patients with airway disease.

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

Treatment

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

Further absorption should be prevented using appropriate methods, e.g. treatment within 1–2 hours with activated charcoal. If activated charcoal is used, airway protection is imperative for drowsy patients. In cases of mixed overdose where no more than an hour has elapsed since ingestion, gastric lavage may be considered, but not as a routine measure.

If CNS biological functions are severely reduced, use of the benzodiazepine antagonist flumazenil (Anexate®) may be considered. This should only be administered under closely monitored conditions. Because of its short half-life (about 1 hour), patients given flumazenil will require further monitoring once its effects have worn off. Flumazenil must not be administered to patients receiving drugs that lower the seizure threshold (e.g. tricyclic antidepressants). Please 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.

Properties and effects

ATC code: N03AE01

Mechanism of action/pharmacodynamics

Clonazepam possesses pharmacological properties that are common to all benzodiazepines, including sedative, muscle-relaxing, anxiolytic and, in particular, anticonvulsant effects.

The central actions of benzodiazepines are mediated through an enhancement of 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 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-wave discharge in absence seizures (petit mal), slow spike-wave complex, generalised spike-wave complex, spikes in the temporal region or at other locations, and irregular spikes and waves.

Generalised EEG abnormalities are more regularly suppressed than focal abnormalities. Accordingly, clonazepam shows an effect in generalised and focal epilepsies.

Clinical efficacy

Clinical studies are available for the following forms of epilepsy:

Petit-mal: > 400 patients, including children, including a double-blind study.

Lennox (-Gastaut) syndrome: > 400 patients, including a double-blind study.

Myoclonic seizures: approx. 100 patients, including a double-blind crossover study vs. placebo, several uncontrolled studies.

Atonic epilepsy (drop syndrome): one single-blind and several open studies.

West syndrome (infantile spasms): > 200 observations, children.

Status epilepticus (with various types of seizure): approx. 600 observations.

These studies establish the indication for the use of clonazepam in various types of epilepsy as stated in *Indications and potential uses.*

Pharmacokinetics

Absorption

The active substance clonazepam is rapidly and almost completely absorbed after oral administration of the tablets. Peak blood concentrations are reached in most cases within 1–4 hours of ingestion. The absorption half-life is around 25 minutes. Mean absolute bioavailability after oral administration is around 90%, with large differences between

individual patients. Rivotril tablets are bioequivalent to the oral solution with respect to the extent of clonazepam absorption, although the rate of absorption is somewhat lower for the tablets.

Plasma concentrations of clonazepam at steady state on once-daily dosing are 3-fold higher than after a single oral dose; the predicted accumulation ratios for twice- and three-times-daily dosing are 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily, steady-state predose plasma concentrations of clonazepam averaged 55 ng/ml. The plasma concentration-dose relationship of clonazepam is linear. Anticonvulsant plasma levels of clonazepam are in the target range of 20 to 70 ng/ml.

Most patients with steady-state plasma concentrations above 100 ng/ml developed severe toxic effects, including increased seizure frequency.

After i.m. administration, t_{max} is approximately 3 hours and absolute bioavailability 93%.

Irregularities in the absorption profiles of clonazepam are occasionally observed after i.m. administration.

Distribution

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

The distribution half-life is approximately 0.5–1 hour. The volume of distribution of clonazepam averages 3 l/kg. Plasma protein binding is 82–86%.

A single oral dose of 2 mg 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 i.v. dose has an immediate effect which lasts for 2–3 hours.

Metabolism

Clonazepam is largely metabolised by reduction to 7-aminoclonazepam and by N-acetylation to 7-acetamidoclonazepam. Hydroxylation at the C-3 position also occurs. The liver enzyme cytochrome P-450 3A4 is involved 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. Clearance is almost 55 ml/min irrespective of gender, but weight-normalised values declined with increasing body weight.

Fifty to 70% of the dose is excreted as metabolites in the urine, and 10–30% in the feces. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose.

Pharmacokinetics in special patient groups
Renal impairment

Renal impairment does not affect the pharmacokinetics of clonazepam. Based on the pharmacokinetic criteria, no dose adjustment is generally required in patients with renal impairment. Regular monitoring of individual renal function parameters is, however, required.

Hepatic impairment

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

Although the influence of hepatic disease 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 have not been investigated.

As with other benzodiazepines, plasma elimination of clonazepam may be delayed in elderly patients or those with hepatic impairment. This should be borne in mind when selecting the dose of Rivotril. The pharmacological effects of benzodiazepines 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.

Pediatric patients

Overall, the elimination kinetics in children are similar to those 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, administration of 0.10 mg/kg led to concentrations of 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. Clearance values in neonates are dependent on postnatal age.

Elimination half-life values in neonates are of the same magnitude as the limits found for adults.

In children, clearance values of 0.42 ± 0.32 ml/min/kg (age group 2 18 years) and 0.88 ± 0.4 ml/min/kg (age group 7 12 years) were reported; these values decreased with increasing body weight. A ketogenic diet in children does not affect clonazepam concentration.

Preclinical data

Carcinogenicity
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 with in-vitro or host-mediated metabolic activation revealed no genotoxic effects of clonazepam.

Reproductive toxicity
Studies assessing fertility and general reproductive performance in rats showed a reduced pregnancy rate and increased postnatal mortality at doses of 10 and 100 mg/kg/day.

Teratogenicity
No adverse effects on the dams or on embryofetal development were observed in either mice or rats following administration of oral clonazepam during organogenesis at doses of up to 20 and 40 mg/kg/day, respectively.

In several rabbit studies a small non-dose-dependent increase in similar malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed following clonazepam doses of up to 20 mg/kg/day (see under *Pregnancy and lactation, Lactation*).

Additional information

Incompatibilities

Sodium bicarbonate solution must not be used for dilution, as precipitation may occur (see *Dosage and administration*).

Stability

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

Once the bottle has been opened, Rivotril drops are stable for 120 days at room temperature (15–25°C).

Special instructions for storage

Rivotril oral drops:	Do not store above 25°C.
Rivotril tablets:	Do not store above 30°C. Store in the original pack in order to protect content from light.
Rivotril ampoules:	Do not store above 30°C. Store in the original pack in order to protect content from light.

Instructions for use and handling

The concentrate of 1 ml containing 1 mg of active ingredient may be used only after addition of 1 ml of diluent in order to avoid local irritation of the veins. The injection syringe then contains 2 ml of ready-to-use injection solution with 1 mg of active substance (concentration: 0.5 mg/ml). The injection solution should be prepared immediately before use. Intravenous administration should be very slow, with continuous monitoring of EEG, respiration, and blood pressure.

In order to avoid precipitation, Rivotril can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg active substance ampoule) to at least 85 ml (e.g. 3 ampoules in 250 ml): 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 clonazepam can be adsorbed on plastics, especially PVC. It is therefore recommended that alternative materials be used. If PVC bags are used the mixture should be infused immediately and as a rule within 4 hours. The infusion time should not exceed 8 hours (see *Dosage and administration, Parenteral administration, Special dosage instructions*).

Packs

Oral drops 2.5 mg/ml	10 ml
Tablets 0.5 mg	50
Tablets 2 mg	30
Ampoule pack containing:	
Ampoules 1 mg/1 ml solution	5
Ampoules (1 ml) sterile water for injections as diluent, to be mixed before i.v. or i.m. injection	5

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

Current at July 2018

Drops:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Delpharm Milano S.r.l., Segrate, Italy

Tablets:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by Recipharm Leganés S.L.U., Leganés, Spain

Ampoules:

Made for F. Hoffmann-La Roche Ltd, Basel, Switzerland

by CENEXI SAS, Fontenay-sous-Bois, France