SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rivotril 0.5 mg tablets
Rivotril 2 mg tablets
Rivotril 2.5 mg/mL oral drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rivotril 0.5 mg tablets. One tablet contains: clonazepam 0.5 mg.
Rivotril 2 mg tablets. One tablet contains: clonazepam 2 mg.
Rivotril 2.5 mg/mL oral drops solution. 1 mL of the drop solution contains: clonazepam 2.5 mg (1 drop = approximately 0.1 mg active substance).

Excipients with known effects
Rivotril 0.5 mg tablets and 2 mg tablets contain lactose.
Rivotril 2.5 mg/mL oral drops solution contains sodium, benzyl benzoate (contained in peach flavouring) and propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Rivotril is available as tablets and as oral drops, solution.
The tablet may be divided into equal doses.

4. CLINICAL INFORMATION

4.1 Therapeutic Indications

Most clinical forms of epilepsy in infants and children. In particular:
- typical or atypical petit mal disease;
- generalised, primary or secondary tonic-clonic seizures;
- status of disease in all its clinical forms.

Rivotril is also indicated in adult epilepsy and focal seizures.

4.2 Posology and method of administration

The dosage of Rivotril is mostly individual and must be established case by case on the basis of clinical response and tolerance.

Before adding Rivotril to an existing anticonvulsant treatment, it should be considered that the use of several anticonvulsants may lead to an increase in side effects.

Posology
To avoid side effects at the start of treatment, it is necessary to gradually increase the daily dose until the maintenance dose has been reached.

The initial dose **for infants and children up to 10 years of age (or up to 30 kg in weight**) is 0.01-0.03 mg/kg/day to be divided into 2-3 doses. The dose should be increased by no more than 0.25-0.5 mg, every third day, until a daily maintenance dose of about 0.1 mg/kg is reached or seizures are controlled or unwanted effects preclude further increases.

In children, the maximum daily dose, not to be exceeded, is 0.2 mg/kg.

Based on the established dosage for children up to 10 years of age (or up to 30 kg in weight) and adults (below), the recommended starting dose for **children and adolescents between 10 and 16 years of age** is 1-1.5 mg/day to be divided into 2-3 doses. The dose can be increased by 0.25-0.5 mg every third day until the individual maintenance dose is reached (usually 3-6 mg/day).

The initial dose for **adults** should not exceed 1.5 mg/day to be divided into 3 doses. The dose may be increased in increments of 0.5 mg, every three days, until convulsive seizures are adequately controlled or unwanted effects preclude further increases.
The maintenance dose must be established individually for each patient on the basis of response. A maintenance dose of 3-6 mg/day is usually sufficient.

In adults, the maximum therapeutic dose, which must not be exceeded, is 20 mg.

The daily dose should be divided into 3 equal doses. If the doses cannot be divided equally, the larger dose should be taken before going to bed.
The maintenance dose should be achieved after 1-3 weeks of treatment.

To make it easier to adapt the dosage to individual needs and to provide an easy way of dividing up the total daily dose, it is recommended to use Rivotril drops (1 drop = approx. 0.1 mg active substance) in infants and 0.5 mg tablets in adults in the initial phase of treatment.

The drops should be administered with a spoon or may be mixed with water, tea or fruit juice.

To assist administration, 0.5 mg Rivotril tablets can be divided into equal halves, while 2 mg tablets can be divided into equal halves or quarters.
The tablets have a breakline to allow lower doses to be administered. To break the tablet, hold it with the fracture line facing upwards and apply downward pressure.

Elderly patients
In elderly patients, the lowest possible dose should be used and special care should be taken during the initial titration phase.
In the treatment of elderly patients, the dosage must be carefully established by the doctor, who will have to consider a possible reduction in the above dosages.

Renal impairment
The safety and efficacy of clonazepam in patients with renal failure have not been studied; however, based on pharmacokinetic criteria, no dosage adjustment is required in these patients (see section 5.2).

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

Epilepsy
Clonazepam may be administered with one or more anti-epileptic agents. In these cases, the dose of each medicine must be adjusted to achieve the optimal effect.
As with all anti-epileptic drugs, treatment with clonazepam should not be discontinued suddenly, but should be reduced gradually (see section 4.8).

How to use the dropper bottle
Hold the bottle vertically, with the opening facing downwards. If the liquid does not flow down, turn the bottle upside down several times, or shake it gently.

Caution: Do not pour Rivotril drops into the mouth directly from the bottle. After each opening, ensure that the dropper is locked onto the neck of the bottle.

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4.3 Contraindications

Hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1. The use of Rivotril is contraindicated in patients with severe hepatic impairment, as benzodiazepines may lead to hepatic encephalopathy.
It can be used in subjects with open-angle glaucoma receiving appropriate treatment, but is contraindicated in acute angle-closure glaucoma.
The product is also contraindicated in severe renal failure and severe respiratory failure.
Do not administer in the first trimester of pregnancy.
Rivotril should not be used in comatose patients, or in patients with known pharmacological, drug or alcohol abuse.

4.4 Special warnings and precautions for use

During treatment with clonazepam, a loss of efficacy may occur.

Hepatic impairment
Benzodiazepines play a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. Special care must be taken when administering Rivotril to patients with mild to moderate hepatic impairment (see section 4.3).

CNS, psychosis and depression
Rivotril should be used with special care in patients with ataxia.

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

Suicidal ideation and behaviour have been reported in a number of situations in patients treated with anti-epileptic drugs. A meta-analysis of randomised, placebo-controlled trials of anti-epileptic drugs showed a slightly increased risk of suicidal ideation and behaviour. The mechanism of this risk is unknown and the available data do not exclude the possibility of an increased risk for clonazepam.

Therefore, patients presenting with signs of suicidal ideation and behaviour should be monitored and appropriate treatment considered. Patients (and their carers) should be advised to be alert should such signs emerge.

Patients with a history of depression or attempted suicide should be kept under close observation.

Myasthenia gravis
As with any substance that has CNS depressant and/or muscle relaxant properties, special care must be taken when administering Rivotril to patients with myasthenia gravis.

Psychiatric and "paradoxical" reactions

It is known that, when benzodiazepines are used, paradoxical reactions may occur, such as restlessness, agitation, irritability, aggression, anxiety, delirium, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other negative effects in behaviour. If this occurs, the use of the drug must be discontinued. Paradoxical reactions occur more easily in children and the elderly.

The risk of withdrawal symptoms is increased when benzodiazepines are used with daily sedatives (cross-tolerance).

Respiratory diseases
Due to possible respiratory depression, Rivotril should be used with caution in patients with chronic

respiratory diseases (e.g. chronic obstructive pulmonary disease).
The dose of Rivotril must be promptly adjusted according to individual requirements in patients with pre-existing respiratory (e.g. chronic obstructive pulmonary disease) or liver disease and in patients treated with other centrally acting drugs (see section 4.5). Effects on the respiratory system may be aggravated by a pre-existing airway obstruction or brain damage, or if other drugs capable of depressing respiratory function have been administered. As a rule, this effect can be avoided by individual dose adjustment.

Epilepsy
The dose of Rivotril must be promptly adjusted according to individual requirements in patients treated with other centrally acting drugs or anticonvulsant (anti-epileptic) agents (see section 4.5). When used in individuals with multiple forms of convulsions, Rivotril may increase the incidence or induce the onset of generalised tonic-clonic seizures (grand mal seizures). The addition of suitable anticonvulsants or an increase in their dosage may therefore be provided. Concomitant use of valproic acid and Rivotril may produce an absence status.
In predisposed individuals, if treated with clonazepam at high doses and for prolonged periods, they may become addicted, as is the case with other drugs with hypnotic, sedative and tranquilising activity.

In epileptic patients anticonvulsant drugs including Rivotril should not be discontinued suddenly as they may precipitate epileptic illness. When the need to reduce the dose or discontinue it emerges in the clinician's judgement, this should be done gradually. In such cases a combination with other anti-epileptic drugs is indicated.

In some forms of epilepsy an increase in the frequency of seizures is possible (see section 4.8) with long-term treatment.

As a rule, epilepsy patients are not allowed to drive. Although adequately controlled with Rivotril, it must be remembered that any increase in dosage or change in the timing of intake may alter patients' reactions according to individual susceptibility (see section 4.7).

Abuse and addiction
The use of benzodiazepines may lead to the development of physical and psychological dependence (see section 4.8). Abuse has been reported in drug abusing patients.
Prolonged or high-dose treatment may lead to reversible disorders such as dysarthria, reduced coordination of movements, gait disturbances (ataxia), nystagmus and double vision (diplopia). Once physical dependence has developed, the abrupt end of treatment will be accompanied by withdrawal symptoms. During long-term treatment, withdrawal symptoms may develop after a long period, especially with high doses or if the daily dose is reduced rapidly or if treatment is stopped suddenly. Symptoms include trembling, sweating, agitation, sleep disturbances and anxiety, headache, diarrhoea, muscle pain, extreme anxiety, tension, restlessness, mood changes, confusion, irritability and epileptic seizures that may be associated with the underlying pathology. In severe cases, the following symptoms may occur: de-realisation, de-personalisation, 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 sudden discontinuation of treatment, abrupt discontinuation of the drug should be avoided and treatment, even if only short-lived, should be terminated by gradually reducing the daily dose.

Amnesia
The risk of anterograde amnesia, which can occur with the use of benzodiazepines at therapeutic doses, increases for higher dosages. The amnesic effect may be associated with behavioural abnormalities and in certain forms an increased frequency of convulsions.

Sleep apnoea
Benzodiazepines are not recommended in patients with sleep apnoea due to possible additional effects on respiratory depression.

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Sleep apnoea appears to be more common in patients with epilepsy and the relationship between sleep apnoea, the occurrence of seizures and post-ictal hypoxia must be considered in light of respiratory depression and benzodiazepine-induced sedation. Therefore, Rivotril should only be used in epileptic patients with sleep apnoea when the expected benefit outweighs the potential risk.

Concomitant use of alcohol/CNS depressants
Concomitant use of Rivotril with alcohol and/or drugs with central nervous system depressant activity should be avoided. Such concomitant use may increase the clinical effects of Rivotril, including possible deep sedation (which may lead to coma and death) and clinically relevant respiratory and/or cardiovascular depression (see sections 4.5 and 4.9).

Risk of concomitant opioid use
Concomitant use of Rivotril and opioids may lead to sedation, respiratory depression, coma and death. As a result of these risks, the concomitant prescription of sedatives such as benzodiazepines and related drugs such as Rivotril and opioids should be limited to patients in whom alternative treatment options are not possible. If it is decided to prescribe Rivotril concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendations in section 4.2).
Patients should be closely followed for signs and symptoms of respiratory depression and sedation. In this regard, it is strongly recommended that patients and their carers (where applicable) be informed of these symptoms (see section 4.5).

Alcohol in any form can cause seizures regardless of treatment; it is therefore imperative that patients on Rivotril treatment refrain from consuming alcoholic beverages. In combination with Rivotril, alcohol may alter the effects of the drug, impair the results of treatment or cause unpredictable side reactions.

Medical history of alcohol or drug abuse
People prone to drug addiction, such as alcoholics and drug addicts, should be closely monitored when taking Rivotril because of their predisposition to develop a habit and dependence.

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

Porphyria
Clonazepam should be administered with caution in patients with porphyria, as it may have a porphyrogenic effect.

Elderly patients

The pharmacological effects of benzodiazepines appear to be greater in elderly patients than in younger patients, even at similar plasma concentrations of benzodiazepines, probably due to age-related differences in drug-receptor interaction, post-receptor mechanisms and organ function.

Paediatric use
In infants and children, Rivotril may cause increased production of saliva and bronchial secretions. Therefore, special care must be taken to keep the airways clear.

Other special warnings and precautions for use
As Rivotril can lead to increased salivation, this should be taken into account before prescribing the drug to patients who have difficulty controlling their secretions. During prolonged treatment with Rivotril it is advisable to carry out complete blood counts and liver function tests periodically.
The combination with other psychotropic drugs requires special care and vigilance on the part of the physician in order to avoid unexpected side effects of interaction.
Rivotril should be used with caution in patients with sleep apnoea, chronic pulmonary insufficiency or impairment of renal and hepatic function, the elderly and debilitated individuals. In such a case, the dose should generally be reduced.

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As Rivotril metabolites are excreted via the urinary tract, the drug should be administered with caution in patients with impaired renal function in order to avoid excessive accumulation.

Important information about some of the excipients
Tablets contain **lactose** so patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Oral drops, solution contains:
Sodium
This medicine contains less than 1 mmol (23 mg) of sodium per 1 mL, i.e. it is essentially "sodium-free".

Benzyl benzoate (contained in peach flavouring)
This medicine may contain a maximum of 0.48 mg benzyl benzoate per drop of medicine. Benzoates can lead to increased bilirubinaemia due to the detachment of bilirubin from albumin, which can increase neonatal jaundice and evolve into kernicterus (deposits of unconjugated bilirubin in brain tissue).

Propylene glycol
This medicine contains approximately 40 mg propylene glycol per drop of medicine.
Co-administration with any alcohol dehydrogenase substrate such as ethanol may induce serious adverse effects in infants and children under 5 years of age.
Although propylene glycol has shown no toxic effects on reproduction and development in animals or humans, it can reach the fetus and has been found in breast milk. As a consequence, the administration of propylene glycol to pregnant or lactating patients must be considered on a case-by-case basis.
Clinical monitoring is required for patients with liver or kidney failure due to various adverse events attributed to propylene glycol such as renal dysfunction (acute tubular necrosis), acute kidney damage and liver dysfunction.

4.5 Interactions with other medicinal products and other forms of interaction

Rivotril may be administered with one or more anti-epileptic agents. The likelihood of pharmacokinetic interactions with these other drugs is low.
Nevertheless, the addition of an additional anti-epileptic drug to a patient's treatment regimen should include prompt assessment of treatment response due to more likely side effects such as sedation and apathy. In such cases, the dose of each drug must be adjusted in order to achieve the optimal desired effect.

Pharmacokinetic interactions between drugs

The anti-epileptic drugs phenytoin, phenobarbital, carbamazepine, lamotrigine and, to a lesser extent, valproate may increase the clearance of clonazepam and thus reduce its plasma concentrations by up to 38% in combination treatments.

Rivotril may affect phenytoin concentrations. Given the bi-directional nature of the clonazepam-phenytoin interaction, unmodified phenytoin levels have been found to increase or decrease after co-administration with Rivotril, depending on dosage and patient-related factors. Concomitant treatment with primidone may alter plasma concentrations of primidone (usually increased).

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

Selective serotonin re-uptake inhibitors, such as sertraline (weak CYP3A4 inducer), fluoxetine (CYP2D6 inhibitor) and the anti-epileptic drug felbamate (CYP2C19 inhibitor, CYP3A4 inducer), do not alter the pharmacokinetic parameters of clonazepam in combination.

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Pharmacodynamic interactions between drugs

When Rivotril is used in combination with drugs that depress the CNS, including alcohol, side effects such as sedation and cardio-respiratory depression may increase.

Opioids
Concomitant use of sedative drugs such as benzodiazepines or related drugs such as Rivotril with opioids increases the risk of sedation, respiratory depression, coma and death due to the additive depressant effect on the CNS. The dosage and duration of concomitant use must be limited (see section 4.4).

Alcohol should be avoided in patients receiving Rivotril (see section 4.4).

For warnings on other CNS-depressing drugs, including alcohol, see section 4.9.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
Do not administer in the first trimester of pregnancy; in the remainder of the pregnancy, as well as in early childhood, the drug should only be administered in cases of actual need under the direct supervision of a doctor.
Patients who might become pregnant or are of child-bearing age should be given specialist advice.
The need for anti-epileptic treatment should be reassessed when the patient plans a pregnancy.
The risk of birth defects is increased by a factor of 2 to 3 in offspring of mothers treated with an anti-epileptic; those most frequently reported are cleft lip, cardiovascular malformations and neural tube defects (see section 5.3).
From epidemiological evaluations there is evidence that anticonvulsant drugs have a teratogenic effect. However, it is difficult to determine, based on published epidemiological reports, which drug or combination of drugs is responsible for defects in newborns.

There is also the possibility that other factors, e.g. genetic factors or the epileptic condition itself, may be more important than drug treatment in bringing about birth defects. In view of this, the drug should only be administered to pregnant women if the potential benefit outweighs the risk to the fetus.
Combination therapy with anti-epileptic drugs may be associated with a higher risk of congenital malformations than monotherapy. Therefore, it is important that monotherapy is practised whenever possible.
During pregnancy, Rivotril should only be administered if strictly necessary. The administration of high doses in the last trimester of pregnancy or during labour may cause irregularities in the heartbeat of the unborn child and hypothermia, hypotonia, moderate respiratory depression and poor nutrition in the newborn.
An abrupt interruption of anti-epileptic treatment should not be undertaken because of the danger of a recurrence of epileptic seizures, which could have serious consequences for both mother and child.
Following benzodiazepine use, withdrawal symptoms have occasionally been reported in infants.

Breastfeeding
Since the active ingredient of Rivotril passes into breast milk, breast-feeding should be discontinued.

4.7 Effects on the ability to drive vehicles and use machinery

As Rivotril causes CNS depressant effects, patients treated with this drug should refrain from occupations that require a high degree of vigilance, such as working on machinery or driving motor vehicles.

4.8 Undesirable effects

The most frequent side effects of Rivotril are related to a depressive action on the CNS. Experience has shown that about 50% of patients experience drowsiness and about 30% ataxia: in some cases, these

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complaints may diminish over time.
Behavioural disturbances were detected in about 25% of the patients. Other undesirable effects are listed by system.

Immune system disorders: Allergic reactions and rare cases of anaphylaxis have been reported with benzodiazepines. Hypersensitivity reactions may occur in predisposed individuals.

Endocrine disorders: isolated cases of reversible development of premature secondary sexual characteristics in children (incomplete precocious puberty) have been reported.

Psychiatric disorders: emotional and mood disorders, memory disorders, confusion, disorientation were observed. Depression may occur in patients treated with Rivotril and may also be associated with the underlying disease.
Paradoxical reactions have been observed: restlessness, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, delirium, anger, nightmares and abnormal dreams, hallucinations, psychosis, hyperactivity, inappropriate behaviour and other negative behaviour.
In such cases, use of the drug should be discontinued. Paradoxical reactions are more likely in children and the elderly.
In rare cases, a change in libido may occur.

Nervous system disorders: impaired attention, drowsiness, slowed reactions, muscle hypotonia, tremor, dizziness, ataxia (see section 4.4). These side effects may occur fairly frequently and are usually transient and generally disappear spontaneously during treatment or with dosage reduction. They can be partially prevented by increasing the dosage slowly at the start of treatment.
Rare cases of headache have been observed.
Very rare cases of generalised seizures have been observed.

Reversible disorders such as dysarthria, impaired motor and gait coordination (ataxia) and nystagmus may occur (see section 4.4).
Anterograde amnesia and amnesic effects, which may be associated with behavioural alterations (see section 4.4).
An increased frequency of convulsions with certain forms of epilepsy (see section 4.4).

Eye disorders: reversible vision impairment (diplopia) may occur (see section 4.4).
Common: nystagmus.

Cardiac disorders: palpitations, heart failure including cardiac arrest have been reported.

Thoracic respiratory and mediastinal disorders: respiratory depression may occur (see section 4.4). This effect may be aggravated by pre-existing airway obstruction or brain damage or if other drugs capable of depressing breathing have been administered. As a rule, this effect can be avoided through individual dose adjustment.
Thoracic congestion, rhinorrhoea, breathing disorders, hypersecretion of the upper respiratory tract. In infants and children, increased saliva production or secretion.

Gastrointestinal disorders: the following effects have been reported in rare cases: nausea and epigastric symptoms, appetite disturbances, sialorrhoea, gastrointestinal disturbances, dry mouth, gastritis.

Hepatobiliary disorders: hepatomegaly, transient increase in serum transaminases and alkaline phosphatase.

Haemo-lymphopoietic system disorders: anaemia, leucopenia, thrombocytopenia, eosinophilia.

Skin and subcutaneous tissue disorders: the following effects have been reported in rare cases: urticaria, itching, rash, transient hair loss, pigmentation changes.

Musculoskeletal system and connective tissue disorders: muscle weakness. This side effect may occur

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fairly frequently and is usually transient and generally disappears spontaneously during treatment or with dosage reduction. It can be partially prevented by increasing the dosage slowly at the start of treatment.
(see paragraph 4.4).

Renal and urinary disorders: urinary incontinence may occur in rare cases.

Reproductive system and breast disorders: erectile dysfunction may occur in rare cases.

Systemic disorders and conditions at the site of administration: deterioration of general physical health, hyperthermia, fatigue (tiredness, weakness) (see section 4.4).

Metabolism and nutrition disorders: dehydration, weight changes.

Trauma, poisoning and procedure complications: falls and fractures. The risk of falls and fractures is increased in patients taking concomitant sedatives (including alcoholic beverages) and in elderly patients.

Diagnostic tests: in rare cases, a reduction in platelet count may occur.

Paediatric population
Endocrine disorders: isolated cases of reversible development of premature secondary sexual characteristics (incomplete precocious puberty). (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important, as it allows for the continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus.
When taken alone, an overdose of Rivotril is rarely life-threatening, but can lead to areflexia, apnoea, hypotension, cardiorespiratory depression and coma.
A coma, if it occurs, usually lasts a few hours but may last longer and be cyclical, especially in elderly patients.
With plasma concentrations above therapeutic levels, an increase in the frequency of convulsions may occur.
The respiratory depressant effects associated with benzodiazepines are more serious in patients with respiratory diseases.
Benzodiazepines enhance the effects of drugs with depressive activity on the central nervous system, including alcohol. Symptoms of overdose or intoxication vary greatly from person to person depending on age, body weight and individual response.

Treatment
Monitor the patient's vital signs and define supportive measures in relation to the patient's clinical state. In particular, patients may require symptomatic treatment for effects on the cardiorespiratory system or central nervous system.
Absorption must be prevented by an appropriate method, e.g. treatment with activated charcoal within 1-2 hours. If activated charcoal is used, protect the respiratory tract if the patient is unconscious.
In the event of multiple drug ingestion, gastric lavage should be considered, but not as a routine measure.

In case of severe central nervous system depression, consider using flumazenil, a benzodiazepine

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antagonist. This should only be administered under closely monitored conditions. Flumazenil has a short half-life (about one hour), so patients given it should be monitored after its effects have worn off. Flumazenil should be used with extreme caution in the presence of drugs that may lower the seizure threshold (e.g. tricyclic antidepressants). For more information on the proper use of this medicine refer to the Summary of Product Characteristics for flumazenil.
Caution: flumazenil has no indication in patients with epilepsy treated with benzodiazepines. Antagonism of the benzodiazepine effect may cause convulsions in these patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-epileptic, ATC code: N03AE01

The active ingredient in Rivotril is clonazepam, a benzodiazepine with strong anti-epileptic properties. As with any anti-epileptic drug, the mechanism of action of Rivotril is not exactly known.
The central actions of benzodiazepines are mediated by increasing GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines, the affinity of the GABA receptor for the neurotransmitter is increased through positive allosteric modulation, leading to an increase in the action of released GABA on the transmembrane flux of chloride ions at the postsynaptic level.

There are also data from animal experiments showing an effect of clonazepam on serotonin.

Experimentation in animals and special electroencephalographic investigations in humans have, however, revealed that clonazepam rapidly suppresses many types of paroxysmal activity, including spike-wave discharges in absences (petit mal), slow spike-wave, generalised spike-wave, spikes with temporal or other localisations as well as irregular spike-wave complexes.

Generalised electrocardiogram abnormalities are suppressed with greater regularity than focal abnormalities. Based on this evidence Rivotril therefore favourably influences both focal epilepsy and generalised seizures.

5.2 Pharmacokinetic properties

Absorption
Clonazepam is rapidly and almost completely absorbed after oral administration of Rivotril tablets, and maximum plasma levels of clonazepam are reached within a period of usually 1-4 hours. The absorption half-life is about 25 minutes. Absolute bioavailability is around 90% with large intra-individual differences. Rivotril tablets are bioequivalent to oral solution in terms of the extent of absorption of clonazepam, while the absorption rate is slightly lower with tablets.

Following once-daily administration, steady-state plasma concentrations of clonazepam are 3 times higher than following a single oral administration; the predictable accumulation ratios with the twice- and thrice-daily regimens are 5 and 7, respectively. After multiple oral administrations of 2 mg three times daily, pre-administration steady-state plasma concentrations averaged 55 ng/mL. The dose-response correlation of clonazepam is linear. The target plasma concentration of clonazepam for the anticonvulsant effect is between 20 and 70 ng/mL.
Serious toxic effects, including increased frequency of convulsions, develop more in patients with steady-state plasma concentrations above 100 ng/ml.
After intra-muscular administration, maximum plasma concentrations of clonazepam are reached in about 3 hours, with an absolute bioavailability of 93%. Irregularities in clonazepam absorption profiles have occasionally been observed after intramuscular administration.

Distribution
Clonazepam distributes very rapidly to various organs and tissues, with a preferential distribution in

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brain tissue.

The distribution half-life is about 0.5-1 hour. The distribution volume is 3 l/kg. Binding to plasma proteins is 82-86%.

Biotransformation
Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamino-clonazepam. A hydroxylation at position C-3 is also present. Cytochrome P-450 3A4 is involved in the nitroreduction of clonazepam into pharmacologically inactive or weakly active metabolites.
Metabolites are present in urine as both free and conjugated compounds (glucuronide and sulphate).

Elimination
The average elimination half-life is 30-40 hours and is independent of dose. Clearance is close to 55 mL/min regardless of gender, but normalised values decreased with increasing body weight.

50-70% of the dose is excreted in the urine and 10-30% in the faeces as metabolites. Urinary excretion of unmodified clonazepam is usually less than 2% of the administered dose.

Pharmacokinetics in special populations

Renal damage
Renal damage does not alter the pharmacokinetic parameters of clonazepam. Based on pharmacokinetic criteria, no dosage adjustment is required in patients with renal impairment (see section 4.2).

Hepatic impairment
The binding of clonazepam to plasma proteins in cirrhotic patients is significantly different than in healthy subjects (free fraction 17.1±1.0% vs. 13.9±0.2%). Although the incidence of hepatic impairment on the pharmacokinetics of clonazepam has not been further evaluated, experience with other closely related nitrobenzodiazepines (nitrazepam) indicates that the clearance of unbound clonazepam may be reduced in liver cirrhosis (see section 4.2).

Elderly patients
The pharmacokinetics of clonazepam in elderly populations have not been evaluated.

Paediatric patients
Overall, the elimination kinetics in children are similar to those observed in adults. After therapeutic doses in children (0.03 - 0.11 mg/kg), serum concentrations fell in the same range (13 - 72 ng/mL) as effective concentrations in adults. In infants, doses of 0.10 mg/kg at the end of a short infusion led to concentrations of 28 - 117 ng/mL, dropping to 18 - 60 ng/mL 30 minutes later, which were tolerated without appreciable side effects.
In neonates, clearance values depend on postnatal age.
The elimination half-life in infants is of the same order of magnitude as that observed in adults. Clearance values of 0.42±0.32 mL/min/kg (age 2 - 18 years) and 0.88±0.4 mL/min/kg (age 7 - 12 years) have been reported in children; these values decreased with increasing body weight. The ketogenic diet in children does not affect clonazepam concentrations.

5.3 Pre-clinical safety data

The acute toxicity of clonazepam is very low: in both rats and mice the LD50 is above 4000 mg/kg. Chronic toxicity studies have also shown no pathology attributable to the product, in studies on dogs (3, 10 or 30 mg/kg p.o. 6 days per week for 12 months) and on rats.

Carcinogenicity
No 2-year carcinogenesis studies have been conducted with clonazepam. However, in an 18-month study of chronic administration in rats, no treatment-related histopathological changes were observed

up to the highest tested dose of 300 mg/kg/day.

Mutagenicity
Genotoxicity tests conducted in bacterial systems with in vitro or host-mediated metabolic activation did not indicate a genotoxic potential of clonazepam.

Impairment of fertility
Studies evaluating fertility and general reproductive capacity in rats showed reduced pregnancy rates and reduced survival of newborns with doses of 10 and 100 mg/kg/day.

Teratogenicity
Following oral administration of clonazepam during organogenesis in mice and rats, with doses of up to 20 or 40 mg/kg/day respectively, no maternal or embryo-fetal adverse effects were observed.

In several studies in rabbits, a low, non-dose-dependent incidence of malformations of the same type (cleft palate, palpebral aperture, neural tube and limb defects) was observed following doses of clonazepam up to 20 mg/kg/day (see section 4.6).

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Rivotril 0.5 mg tablets
lactose, maize starch, pregelatinised potato starch, iron oxide red (E172), iron oxide yellow (E172), talc, magnesium stearate.

Rivotril 2 mg tablets
lactose, pregelatinised starch, microcrystalline cellulose, magnesium stearate.

Rivotril 2.5 mg/mL oral drops solution
saccharin sodium, peach flavouring, propylene glycol, glacial acetic acid.

6.2 Incompatibilities

Not relevant

6.3 Shelf life

Rivotril tablets: 5 years.
Rivotril oral drops solution: 3 years

6.4 Special precautions for storage

Rivotril tablets:
This medicine does not require any special storage conditions.

Rivotril oral drops solution:
Do not store at temperatures above 30°C.

6.5 Nature and contents of the container

Rivotril 0.5 mg tablets, Rivotril 2 mg tablets
plastic blister pack laminated with aluminium tape.

Rivotril 2.5 mg/mL oral drops, solution

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20 mL amber glass bottle containing 10 mL of solution, equipped with dropper.
(1 drop = approx. 0.1 mg)

6.6 Special precautions for disposal and other handling

Rivotril 2.5 mg/mL oral drops, solution
Caution: Do not pour Rivotril drops into the mouth directly from the bottle.
After each opening, ensure that the dropper is locked onto the neck of the bottle.

Unused medicine and waste derived from it must be disposed of in accordance with local regulations.

7. MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Arzneimittel GmbH, Ziegelhof 24, 17489 Greifswald, Germany

8. MARKETING AUTHORISATION NUMBER

2.5 mg/mL oral drops solution - 10 mL bottle	MA no. 023159039
20 tablets 0.5 mg	MA no. 023159054
20 tablets 2 mg	MA no. 023159066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation:

2.5 mg/mL oral drops solution - 10 mL bottle	February 1975
20 tablets 0.5 mg	August 1999
20 tablets 2 mg	August 1999

Most recent renewal date: June 2010

10. DATE OF REVISION OF THE TEXT

Subject to the regulation of Presidential Decree no. 309/90 - as amended - Table Medicinal Products Sec. E

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