

Rivotril[®]



Clonazepam

Antiepileptic agent

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antiepileptic agent.

Antipanic agent.

ATC code: N03AE01.

1.2 Type of Dosage Form

Drops

1.3 Route of Administration

Oral: Drops

1.4 Sterile / Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: clonazepam.

2.5 mg/ml (1 drop = 0.1 mg active ingredient).

Excipients: Peach flavour, Saccharin sodium, Brilliant Blue FCF, Acetic acid glacial, Propylene glycol.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Epilepsy.

Panic Disorder.

2.2 Dosage and Administration

Standard Dosage in Epilepsy

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

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

A single oral dose of Rivotril begins to take effect within 30-60 minutes and remains effective for 6-8 hours in children and 8-12 hours in adults.

Oral treatment

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

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

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

Based on established dosages for children up to 10 years (see above) and those for adults (see below) the following can be recommended for children between 10 and 16 years: The initial dose is 1-1.5 mg/day given in 2-3 divided doses. The dose may be increased by 0.25-0.5 mg every third day until the individual maintenance dose (usually 3-6 mg/day) is reached.

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

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

Before adding Rivotril to an existing anticonvulsant regimen, it should be considered that the use of multiple anticonvulsants may result in an increase of undesired effects.

Dosage in Panic Disorder

Adults

The initial dose for adults with Panic Disorder is 0.25 mg twice daily (0.5 mg/day).

An increase to 0.5 mg twice daily (1 mg/day) may be made after 3 days. Subsequent up-titration should be made at intervals of 3 days until Panic Disorder is controlled or until limited by side effects.

The usual maintenance dose is 1 mg twice daily (2 mg/day). A maximum dose of 2 mg twice daily (4 mg/day) may be prescribed in exceptional cases.

Once a stable dose is achieved, patients may switch to a once daily dose, usually taken at bedtime.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use clonazepam for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Treatment should be discontinued gradually, with down-titration of 0.25 mg every 3 days, until the drug is completely withdrawn.

2.2.1 Special Dosage Instructions

Epilepsy and Panic Disorder

Elderly Patients

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

Renal Impairment

The safety and efficacy of clonazepam in patients with renal impairment has not been studied, however based on pharmacokinetic considerations no dose adjustment is required in these patients (see 3.2.5 Pharmacokinetics in Special Populations).

Hepatic Impairment

The safety and efficacy of clonazepam in patients with hepatic impairment has not been studied. No data are available on the influence of hepatic disease on clonazepam pharmacokinetics (see 2.4.1 General (Warnings and Precautions)).

Epilepsy

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

As with all antiepileptic agents, treatment with Rivotril must not be stopped abruptly, but must be reduced in a stepwise fashion (see 2.6 Undesirable Effects).

Panic disorder

Pediatric Patients

The safety and efficacy of clonazepam for the treatment of Panic Disorder in children has not been studied.

2.3 Contraindications

Rivotril must not be used in patients with known hypersensitivity to benzodiazepines or any of the drug's excipients or those with severe respiratory insufficiency or severe hepatic insufficiency. It may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

2.4 Warnings and Precautions**2.4.1 General**

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) or with impairment of renal function.

Concomitant use of alcohol / CNS depressants

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 2.4.4 Interactions with other Medicinal Products and other Forms of Interactions).

Medical history of alcohol or drug abuse

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

For warnings related to the use in infants and small children see 2.5.4 Pediatric Use.

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 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

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 2.4.3 Ability to Drive and Use Machines).

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

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.

Porphyria

In patients with porphyria, clonazepam has to be used with care because it may have a porphyrogenic effect.

2.4.2 Drug Abuse and Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products (see 2.6 Undesirable Effects). 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: derealization, depersonalization, 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.

Ability to Drive and Use Machines

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 (see 2.6 Undesirable Effects).

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Rivotril can be administered concurrently with one or more antiepileptic agents. But adding an extra drug to the patient's regimen should involve a careful evaluation of the response to the treatment, because unwanted effects, such as sedation and apathy are more likely to occur. In such cases, the dosage of each drug must be adjusted to achieve the optimum desired effect.

Pharmacokinetic Drug-Drug Interactions (DDI)

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.

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.

Pharmacodynamic Drug-Drug Interactions (DDI)

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

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.

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

Alcohol should be avoided in patients receiving Rivotril (see 2.4.1 General (Warnings and Precautions)).

See section 2.7 Overdose for warning of other central nervous system depressants, including alcohol.

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

2.5 Use in Special Populations

2.5.1 Pregnancy

From preclinical studies it cannot be excluded that clonazepam possesses the possibility of producing congenital malformations. 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. Under these circumstances, the drug should only be administered to pregnant women if the potential benefits outweigh the risk to the fetus.

During pregnancy, Rivotril may be administered only if there is a compelling indication. Administration of high doses in the last trimester of pregnancy or during labour can cause irregularities in the heartbeat of the unborn child and hypothermia, hypotonia, mild respiratory depression and poor feeding in the neonate. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed 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.

2.5.2 Labor and Delivery

See 2.5.1 Pregnancy.

2.5.3 Nursing Mothers

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.

2.5.4 Pediatric Use

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. See 2.4.1 General (Warnings and Precautions).

2.5.5 Renal Impairment

See 3.2.5 Pharmacokinetics in Special Populations.

2.5.6 Hepatic Impairment

See 2.4.1 General (Warnings and Precautions).

2.6 Undesirable Effects**2.6.1 Clinical Trials**

The adverse experiences for RIVOTRIL are provided separately for patients with seizure disorders and with panic disorder.

Panic Disorder

Data from 3 placebo-controlled clinical trials including 477 patients on active treatment in total are presented in the table below. Adverse Events occurring in $\geq 5\%$ of patients in at least one of the Active Treatment Groups are included.

Table 1 Adverse Events Occurring in $\geq 5\%$ of Patients in at least one of the Active Treatment Groups.

Adverse Event	Placebo (%) (n = 294)	1 to <2 mg/day (%) (n = 129)	2 to <3 mg/day (%) (n = 113)	to >3 mg/day (%) (n = 235)
Somnolence	15.6	42.6	58.4	54.9
Headache	24.8	13.2	15.9	21.3
Upper Respiratory Infection	9.5	11.6	12.4	11.9
Fatigue	5.8	10.1	8.8	9.8
Influenza	7.1	4.7	7.1	9.4
Depression	2.7	10.1	8.8	9.4
Dizziness	5.4	5.4	12.4	8.9
Irritability	2.7	7.8	5.3	8.5
Insomnia	5.1	3.9	8.8	8.1
Ataxia	0.3	0.8	4.4	8.1
Balance loss	0.7	0.8	4.4	7.2
Nausea	5.8	10.1	9.7	6.8
Coordination abnormal	0.3	3.1	4.4	6.0
Lightheaded feeling	1.0	1.6	6.2	4.7

Sinusitis	3.7	3.1	8.0	4.3
Concentration impaired	0.3	2.3	5.3	3.8

Seizure Disorders: The most frequently occurring side effects of Clonazepam are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some may diminish with time; behavior problems have been noted in approximately 25% of patients.

Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, “glassy-eyed” appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

2.6.2 Post Marketing

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

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

Psychiatric Disorders: 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 and vivid dreams.

In rare cases loss of libido may occur.

Dependence and withdrawal, see section 2.4.2 Drug Abuse and Dependence.

Nervous system Disorders: somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia. 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.

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

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

Respiratory Thoracic and Mediastinal System Disorders: Respiratory depression may occur, particularly 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, 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 and epigastric symptoms.

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

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 Disorder: In rare cases urinary incontinence may occur.

Reproductive System and Breast Disorder: 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).

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.

2.7 Overdose

Symptoms

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 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. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

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

Treatment

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

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

If CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Clonazepam exhibits pharmacological properties which are common to benzodiazepines and include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. As with other benzodiazepines these effects are thought to be mediated mainly by post-synaptic GABA mediated inhibition, although there are animal data showing in addition an effect of clonazepam on serotonin. Animal data and electroencephalographic 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, generalized spike wave, spikes with temporal or other locations as well as irregular spikes and waves.

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

3.2 Pharmacokinetic Properties**3.2.1 Absorption**

Clonazepam is rapidly and almost completely absorbed after oral administration. Peak plasma concentrations of clonazepam are reached in 1-4 hours. The absorption half-life is around 25 mins. The absolute bioavailability is 90%.

Plasma concentrations of clonazepam at steady state for a once-daily dosage regimen are 3-fold higher than those after a single oral dose; the predicted accumulation ratios for two times and three times daily regimens are 5 and 7, respectively. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam averaged 55 ng/ml. The plasma concentration-dose relationship of clonazepam is linear. The target anticonvulsant plasma concentrations of clonazepam range from 20 to 70 ng/ml. The threshold plasma concentration of clonazepam in patients with panic disorders is about 17 ng/ml.

3.2.2 Distribution

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

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

3.2.3 Metabolism

Clonazepam is extensively metabolized by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamino-clonazepam. Hydroxylation at the C-3 position also occurs. Hepatic cytochrome P-450 3A4 is implicated in the nitroreduction of clonazepam to pharmacologically inactive metabolites.

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

3.2.4 Elimination

The mean elimination half-life is 30-40 hours. The clearance is 55 ml/min.

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

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

3.2.5 Pharmacokinetics in Special Populations*Renal Failure*

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

Hepatic Failure

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

Elderly

The pharmacokinetics of clonazepam in the old age has not been established.

Neonates

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

3.3 Preclinical Safety**3.3.1 Carcinogenicity**

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

3.3.2 Mutagenicity

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

3.3.3 Impairment of Fertility

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

3.3.4 Teratogenicity

No adverse maternal or embryo-fetal effects were observed in either mice or rats following administration of oral clonazepam during organogenesis, at doses of up to 20 or 40 mg/kg/day, respectively.

In several rabbit studies following doses of clonazepam of up to 20 mg/kg/day, a low, non-dose-related incidence of a similar pattern of malformations (cleft palate, open eyelids, fused sternebrae and limb defects) was observed (see 2.5.1 Pregnancy).

4. PHARMACEUTICAL PARTICULARS**4.1 Storage**

Do not store above 25°C.

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.

4.2 Special Instructions for Use, Handling and Disposal

Not applicable.

4.3 Packs

Drops 2.5 mg/ml

10 ml

4.4 License Holder

Roche Pharmaceuticals (Israel) Ltd., P.O. Box 6391, Hod Hasharon 4524079.

4.5 License Number

Rivotril drops **061.31.21476.00**

Medicine: keep out of reach of children

Manufacturer: Roche S.p.A. Milan, production site Segrate, Italy

1201RIVO0813