SCHEDULING STATUS

S5

PROPRIETARY NAMES AND DOSAGE FORMS

RIVOTRIL® 0,5 mg Tablets

RIVOTRIL® 2 mg Tablets

RIVOTRIL® 1 mg/mℓ Injection

RIVOTRIL® 2,5 mg/mℓ Drops

COMPOSITION

RIVOTRIL contains clonazepam as the active substance.

RIVOTRIL tablets

Each 0,5 mg tablet contains 0,5 mg clonazepam.

Excipients: lactose, maize starch, pregelatinised potato starch, iron oxide red (E172), iron oxide yellow (E172), talc, magnesium stearate.

Each 2 mg tablet contains 2 mg clonazepam.

Excipients: lactose, pregelatinised potato starch, microcrystalline cellulose, magnesium stearate.

RIVOTRIL tablets contain lactose - see WARNINGS AND SPECIAL PRECAUTIONS.

RIVOTRIL injection

Each ampoule contains 1 mg clonazepam per 1 mℓ, and 3 % benzyl alcohol as preservative.

Contains ≈ 15 % *m/v* ethyl alcohol (undiluted ampoule).

RIVOTRIL injection contains benzyl alcohol – see CONTRAINDICATIONS.

1 mℓ water for injection is used as a diluent. After adding the diluent, the solution for injection contains 1 mg clonazepam per 2 mℓ.

RIVOTRIL drops

The drops contain 2,5 mg clonazepam per mℓ, i.e. 1 drop contains 0,1 mg clonazepam.

Excipients: brilliant blue FCF colourant (E133), saccharin sodium, peach flavour, propylene glycol.

PHARMACOLOGICAL CLASSIFICATION

A 2.5 – Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Clonazepam, a benzodiazepine derivative, exhibits pharmacological properties which include anticonvulsive, sedative, muscle relaxing and anxiolytic effects. These effects are thought to be mediated mainly by post-synaptic GABA mediated inhibition.

Electroencephalographic investigations have shown that clonazepam suppresses the spike and wave discharges in absence seizures (petit mal), slow spike wave, generalised spike waves, spikes with temporal or other locations as well as irregular spikes and waves.

Pharmacokinetic properties

Absorption

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

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 regimen is 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 concentrations of clonazepam in patients with panic disorders is about 17 ng/mℓ.

After *IM* administration, maximum plasma concentrations of clonazepam are reached in about 3 hours and the absolute bioavailability is 93 %. Irregularities in the absorption profiles of clonazepam after *IM* administration are occasionally observed.

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 %.

Metabolism

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

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

Elimination

The mean elimination half-life is 30 - 40 hours. The clearance is 55 mℓ/min. The elimination kinetics in children are similar to those observed in adults.

Pharmacokinetics in Special Populations

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

INDICATIONS

RIVOTRIL tablets and RIVOTRIL drops

Epileptic disease

All clinical forms of epileptic disease in infants, children or adults, especially typical or atypical petit mal, focal seizures with elementary or complex symptomatology, generalised primary or secondary tonic-clonic seizures, status epilepticus in all its clinical forms.

Panic disorder

RIVOTRIL is indicated for the treatment of Panic Disorder, with or without agoraphobia.

RIVOTRIL ampoules

Epileptic disease

Status epilepticus in all its forms.

Panic disorder

RIVOTRIL is indicated for the treatment of Panic Disorder, with or without agoraphobia.

CONTRAINDICATIONS

- RIVOTRIL is contraindicated in patients with known hypersensitivity to benzodiazepines.
- Severe respiratory insufficiency
- Acute narrow angle glaucoma
- Myasthenia gravis
- Sleep apnoea

RIVOTRIL ampoules contain benzyl alcohol. Since there have been associated reports of permanent neuropsychiatric deficits and multiple system organ failure associated with benzyl alcohol, administration to neonates, and especially premature infants, must be avoided.

WARNINGS AND SPECIAL PRECAUTIONS

RIVOTRIL may give rise to salivary or bronchial hypersecretion in infants and small children; supervision is thus required to ensure that the airways remain free of secretions.

Drug abuse and dependence

Dependence

There is a potential for abuse. Treatment with RIVOTRIL can lead to physical and psychological dependence on the product. The risk is greater with higher doses; and is particularly pronounced in predisposed patients with a history of alcoholism or drug addiction.

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. The following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of extremities, hypersensivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound effects

A transient syndrome, which may occur in withdrawal of treatment, whereby the symptoms that led to treatment with RIVOTRIL recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Due to the risk of withdrawal symptoms or rebound phenomena, the medicine should - even if only of short duration - be terminated by gradually reducing the daily dose.

Special Precautions

General

RIVOTRIL must be used with care in spinal or cerebellar ataxia, in the event of acute intoxication with alcohol, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic agents, antidepressants or lithium.

Particular caution should be exercised in elderly patients and patients with pre-existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidneys, or who are receiving treatment with other centrally acting medications, barbiturates or anti-convulsant (antiepileptic) agents. These patients require very careful dosage adjustment according to individual requirements. See INTERACTIONS.

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

RIVOTRIL must be used with extreme caution in patients with a history of alcohol or drug abuse. Since alcohol can provoke epileptic seizures, it is imperative that patients abstain from drinking alcohol while under treatment with RIVOTRIL. In combination with RIVOTRIL, alcohol may modify the effects of the medicine, compromise the success of therapy, or give rise to unpredictable side effects.

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

RIVOTRIL may, depending on the dosage, administration and individual susceptibility, modify the patient's reactions (e.g. driving ability, behaviour in traffic). See *Ability to drive and use machines*.

During *IV* administration, a vein of sufficient calibre must be chosen and the injection administered very slowly, with continuous monitoring of respiration and blood pressure. If the injection is too rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

In adults, the rate of injection must not exceed 0,25 - 0,5 mg (0,5 - 1 mℓ of the prepared solution) per minute. See DOSAGE AND DIRECTIONS FOR USE.

Lactose Intolerance

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

Ability to drive and use machines

RIVOTRIL can slow reactions to such an extent that the ability to drive a vehicle or operate machinery is seriously impaired. This effect is increased if the patient has also taken alcohol. Driving, operating machinery or performing other hazardous activities should therefore be avoided. The decision should be made in each case on the basis of the patient's response to treatment and the dosage involved. See SIDE EFFECTS.

INTERACTIONS

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

There is an additive risk of central nervous system depression when central nervous system depressants and RIVOTRIL are taken together.

Pharmacokinetic Interactions

The antiepileptic medicines phenytoin, phenobarbital (phenobarbitone), carbamazepine and sodium valproate may induce the metabolism of clonazepam, causing higher clearance and lower plasma concentrations of the latter during combined treatment.

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

Pharmacodynamic interactions

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

Concurrent use of RIVOTRIL and other centrally acting medications - e.g. other anti-convulsant agents, anaesthetics, hypnotics, psychoactive medicines and some analgesics can produce mutual potentiation of medicine effects. This is especially true in the presence of alcohol. In combination with centrally-acting medications, the dosage of each medicine must be adjusted to achieve the optimum effect.

Epileptic patients must not under any circumstances consume alcohol while being treated with RIVOTRIL, since alcohol may alter the effect of the medicine, reduce the efficacy of treatment or produce unexpected side effects.

PREGNANCY AND LACTATION

Pregnancy

Safety in pregnancy has not been established. Administration of RIVOTRIL 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.

During labour it crosses the placenta and may cause the “floppy-infant” syndrome characterised by central respiratory depression, hypothermia and poor sucking.

Lactation

RIVOTRIL must not be used during breast-feeding, since it passes into the breast milk. If there is a compelling indication for RIVOTRIL, breast-feeding should be discontinued.

DOSAGE AND DIRECTIONS FOR USE

Standard dosage in Epilepsy

Dosage of RIVOTRIL is essentially individual and depends above all on the age of the patient. It will be determined in each patient according to clinical response and tolerance. To ensure optimum dosage adjustment, infants should be given the drops.

The 0,5 mg tablets facilitate the administration of lower daily doses to adults in the initial stages of treatment.

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. An *IV* dose has an immediate effect which lasts for 2 - 3 hours.

Oral treatment

In order to avoid initial side effects, it is essential to increase the daily dose progressively until the maintenance dose suited to the individual patient has been reached.

The initial daily dose for infants and children up to the age of 10 years (or up to 30 kg bodyweight):

Initially 0,01 to 0,03 mg/kg is given in two to three divided doses, the dosage being increased by 0,25 to 0,5 mg every third day, until either a *maintenance* dose of 0,1 mg per kg of bodyweight per day is reached, or until seizures are controlled or side effects prevent a further increase. The daily *maximum* dose in children is 0,2 mg/kg of bodyweight and should not be exceeded.

To obtain optimum adjustment of the dose in infants and children the use of the drop form (1 drop contains 0,1 mg active substance) and the tablets 0,5 mg is recommended. The single-scored 0,5 mg tablet facilitates administration of low doses in the early phase of treatment.

Correct method of administration of RIVOTRIL drops:

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

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

Recommended dose for children between 10 and 16 years: The initial dose is 1 - 1,5 mg per 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: This 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. Usually a maintenance dose of 3 - 6 mg per day is sufficient, but it should be individualised for each patient depending upon response. Maximum recommended daily dose is 20 mg 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 2 to 4 weeks of treatment. Once the maintenance dose level has been reached, the daily amount may be given in a single dose in the evening.

Parenteral treatment

Intravenous administration:

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

Infants and children: Half an ampoule (0,5 mg = 1 mℓ reconstituted solution) by slow intravenous injection or by intravenous infusion.

Adults: One ampoule (1 mg = 2 mℓ reconstituted solution) by slow intravenous injection. This dose can be repeated as required, possibly by intravenous infusion (1 - 4 mg are usually required to reverse the status). In adults, the rate of injection must not exceed 0,25 - 0,5 mg (0,5 - 1,0 mℓ of the prepared solution) per minute and a total dose of 10 mg should not be exceeded.

Slow intravenous injection: The 1 mℓ ampoule solution containing 1 mg active ingredient may only be employed after addition of 1 mℓ diluent in order to avoid local irritation to the veins. A vein of sufficient calibre must be chosen. The injection solution should be prepared immediately before use. Intravenous injection should be administered slowly with continuous monitoring of ECG, respiration and blood pressure. If the injection is rapid or the calibre of the vein is insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

Intravenous infusion: RIVOTRIL (only the ampoule with the active substance) can be diluted for infusion with the following media in a ratio of 1 ampoule (1 mg) to at least 85 mℓ (e.g. 3 ampoules in 250 mℓ) to avoid precipitation: sodium chloride 0,9 %; sodium chloride 0,45 % +

glucose 2,5 %; glucose 5 % and glucose 10 %. These mixtures are stable for 24 hours at room temperature.

The active ingredient can be absorbed on polyvinyl chloride (PVC). It is therefore, recommended that either glass containers be used or, if PVC bags are employed, that the mixture be infused immediately and usually within 4 hours. The infusion time should not exceed 8 hours.

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

Intramuscular administration: The intramuscular route should only be used by way of exception or if *IV* administration is not feasible. (After intramuscular injection T_{max} is 3 hours).

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 the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances the dose may be increased in increments of 0,125 to 0,25 mg twice a day, every 3 days until panic disorder is controlled or until side-effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0,125 mg twice a day every 3 days, until the medicine is completely withdrawn.

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 RIVOTRIL for extended periods should periodically re-evaluate the long-term usefulness of the product for the individual patient.

Paediatric Patients: There is no clinical trial experience with RIVOTRIL in panic disorder patients under 18 years of age.

Geriatric Patients: There is no clinical trial experience with RIVOTRIL in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of RIVOTRIL and observed closely. See WARNINGS AND SPECIAL PRECAUTIONS.

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 *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.

Epilepsy

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

Treatment with RIVOTRIL must not be stopped abruptly, but be reduced in a stepwise fashion. See SIDE EFFECTS AND WARNINGS AND SPECIAL PRECAUTIONS.

RIVOTRIL tablets 0,5 mg can be divided into equal halves to facilitate dosing. RIVOTRIL tablets 2 mg can be divided into equal halves or quarters to facilitate dosing.

Panic disorder

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

SIDE EFFECTS

The following side-effects have been reported but frequencies are unknown:

Epilepsy*:*

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

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 ≥ 5 % of patients in at least one of the Active Treatment Groups are included - see Table 1 below.

Table 1: Adverse Events Occurring in ≥ 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)	> 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
Abnormal coordination	0,3	3,1	4,4	6,0
Light-headed feeling	1,0	1,6	6,2	4,7
Sinusitis	3,7	3,1	8,0	4,3
Impaired concentration	0,3	2,3	5,3	3,8

Post-Marketing

Epilepsy and Panic Disorder

Blood and lymphatic system disorder: Thrombocytopenia (reduction in blood platelets).

Immune system disorders: Allergic reactions and cases of anaphylaxis have been reported to occur with RIVOTRIL.

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, confusion, disorientation have been observed. Depression may occur in patients treated with RIVOTRIL, but it may be also associated with the underlying disease. The following paradoxical reactions have been observed: excitability, irritability, aggressive behaviour, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams. In rare cases decrease in sexual drive (loss of libido) may occur.

Nervous system disorders: Somnolence (sleepiness), confusion, slowed reaction, muscular hypotonia, dizziness (light headedness), ataxia. These effects can be partially prevented by increasing the dose slowly at the start of treatment. Headache has been observed. Particularly in long-term or high-dose treatment, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of movements and gait (ataxia) and disorders of vision

(double vision, nystagmus) may occur. Anterograde amnesia may occur using RIVOTRIL at therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour. With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment has been observed.

Eye Disorder: Particularly in long-term or high-dose treatment, reversible disorders of vision (double vision) have occurred.

Vascular disorder: If the injection is rapid or the calibre of the vein insufficient, there is a risk of thrombophlebitis, which may in turn lead to thrombosis.

Respiratory thoracic and mediastinal system disorders: Respiratory depression has occurred, particularly on *IV* administration of clonazepam. This effect was aggravated by pre-existing airways obstruction or brain damage or if other medications which depress respiration were given. As a rule, this effect should be avoided by careful adjustment of the dose to individual requirements. In infants and young children, RIVOTRIL has caused increased production of saliva and bronchial secretion. Particular attention should therefore be paid to maintaining patency of the airways.

Gastrointestinal disorders: Nausea and epigastric symptoms.

Skin and subcutaneous tissue disorders: Urticaria, pruritus, rash, transient hair loss, pigmentation changes.

Musculoskeletal and connective tissue disorders: Muscle weakness, this undesirable effect is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It may be partially prevented by increasing the dose slowly at the start of treatment.

Renal and urinary disorder: Urinary incontinence.

Reproductive system and breast disorder: Erectile dysfunction (impotence).

General disorders and administration site conditions: Fatigue (tiredness lassitude), this undesirable effect is usually transient and generally disappears spontaneously in the course of the treatment or on reduction of the dosage. It could 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: An increased risk for falls and fractures has been recorded in elderly RIVOTRIL users.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Benzodiazepines such as RIVOTRIL, commonly cause drowsiness, confusion, ataxia, dysarthria and nystagmus. Coma, hypotension, cardiovascular and respiratory depression occasionally occur but are seldom serious if these medicines are taken alone. Coma, if it occurs, usually lasts only 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.

If CNS depression is severe, a benzodiazepine antagonist such as flumazenil may be considered (see package insert of flumazenil). This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil, for further information on the correct use of this product.

Warning: The benzodiazepine antagonist, flumazenil, is not indicated in patients with epilepsy who have been given benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

In small children it is important to watch the airways due to possible hypersalivation and disturbance of swallowing. Excitation and hyperactivity may appear during recovery phase.

IDENTIFICATION

RIVOTRIL ampoules: 1 mg clonazepam in 1 mℓ solvent, each accompanied by an ampoule containing 1 mℓ water for injection as a diluent.

RIVOTRIL drops 2,5 mg/mℓ: Clear to almost clear blue solution contained in 10 mℓ amber glass dropper bottles.

RIVOTRIL tablets 0,5 mg: - orange, single-scored tablets imprinted "ROCHE 0.5".

RIVOTRIL tablets 2 mg: - white to slightly yellowish, double-scored tablets imprinted "ROCHE .2." (with dot before and after the 2).

PRESENTATIONS

RIVOTRIL ampoule pack: 5 ampoules with 1 mg substance in 1 mℓ solvent and 5 ampoules 1 mℓ water for injection as diluent to be mixed immediately before *IM* or *IV* injection.

The 1 mℓ ampoule solution containing 1 mg active substance may only be employed after addition of 1 mℓ diluent. (After the addition of the diluent, the injection solution contains 1 mg clonazepam per 2 mℓ). The injection solution should be prepared immediately before use.

RIVOTRIL drops 2,5 mg per mℓ: (1 drop contains 0,1 mg active substance) in a 10 mℓ amber glass dropper bottle.

RIVOTRIL tablets 0,5 mg in packs of 60's, 90's and 100's.

RIVOTRIL tablets 2 mg in packs of 60's, 90's and 100's.

STORAGE INSTRUCTIONS

Store at or below 30 °C and in the original package, protected from light.

RIVOTRIL should not be used after the expiry date shown on the container.

Store out of reach of children.

REGISTRATION NUMBERS

RIVOTRIL 1 mg/mℓ (Injection)	F/2.5/187
RIVOTRIL 2,5 mg/mℓ (Drops)	F/2.5/188
RIVOTRIL 0,5 mg (Tablets)	F/2.5/189
RIVOTRIL 2 mg (Tablets)	F/2.5/190

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

Roche Products (Pty) Ltd

24 Fricker Road

Illovo

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

DATE OF PUBLICATION OF THIS PACKAGE INSERT

Registration: 6 January 1975

Last revision: 19 March 2010**,** 4 February 2015