PACK INSERT FOR MALAYSIA

Rivotril®

Clonazepam

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Antiepileptic agent

1.2 Type of Dosage Form

Tablets

1.3 Route of Administration

Oral

1.4 Qualitative and Quantitative Composition

Active ingredient: clonazepam.

Tablets:

0.5 mg (break-mark) and 2 mg (cross-break-mark)

The tablets are cylindrical, biplanar and of a white to slightly yellowish colour (2 mg) or of a pale orange colour (0.5 mg).

Rivotril tablets contain lactose. For warning related to lactose, see 2.4.1 General (Warnings and Precautions)).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

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

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

2.2 Dosage and Administration

The dosage of Rivotril must be individually adjusted according to the patient's clinical response and tolerance. 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. Tablets are scored to allow administration of lower doses. To break the tablet, hold it with the score facing up and apply downward pressure.

Standard dosage in Epilepsy

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

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 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.

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.

2.2.1 Special Dosage Instructions

Elderly Patients:

The lowest possible dose should be used in the elderly (see 2.5.5 Use in Special Populations; Geriatric Use) and particular care should be taken during up-titration.

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:

Patients with severe hepatic impairment should not be treated with clonazepam (see section 2.3 Contraindications). Patients with mild to moderate hepatic impairment should be given the lowest dose possible.

Epilepsy

Clonazepam 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 clonazepam must not be stopped abruptly, but must be reduced in a stepwise fashion (see 2.6 Undesirable effects).

2.3 Contraindications

Rivotril is contraindicated in patients with known hypersensitivity to clonazepam or any of the drug's excipients, and in patients with severe respiratory insufficiency or severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.

Rivotril tablets are contraindicated in patients with a medical history of sleep apnoea for the treatment of panic disorders.

2.4 Warnings and Precautions

2.4.1 General

Some loss of effect may occur during the course of clonazepam treatment.

Hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. Special caution should be exercised when administering Rivotril to patients with mild to moderate hepatic impairment (see 2.3 Contraindications).

CNS, psychosis and depression

Rivotril should be used only with particular caution in patients with ataxia. Benzodiazepines are not recommended for the primary treatment of psychoic illness. Patients with a history of depression and/or suicide attempts should be kept under close supervision.

Myasthenia gravis

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Rivotril to a patient with myasthenia gravis.

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 that could result in coma or death, clinically relevant respiratory and/or cardio-vascular depression (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interactions and 2.7 Overdose).

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

Psychiatric and 'paradoxical' reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behavior and other adverse behavioral effects are known to occur when using benzodiazepines (see section 2.6.2 Post Marketing). Should this occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

Amnesia

Anterograde amnesia may occur using benzodiazepines at therapeutic dosages, the risk increasing at higher dosages.

Sleep apnoea

Benzodiazepines are not recommended for use in patients with sleep apnoea due to possible additive effects on respiratory depression. Sleep apnoea appears to be more common in patients with epilepsy and the relationship between sleep apnoea, seizure occurrence and post-ictal hypoxia needs to be considered in light of benzodiazepine-induced sedation and respiratory depression. Therefore, Rivotril should only be used in epileptic patients with sleep apnoea when the expected benefit exceeds the potential risk.

Respiratory disorders

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).

Epilepsy

The dosage of Rivotril must be carefully adjusted to individual requirements in patients undergoing treatment with other centrally acting medications or anticonvulsant (antiepileptic) agents (see 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction).

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.

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Porphyria

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

Risks from Concomitant Use with Opioids

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Rivotril with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Rivotril is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (see 2.4.4 Interactions with other Medicinal Products and other Forms of Interaction).

2.4.2 Drug Abuse and Dependence

Use of benzodiazepines may lead to the development of physical and psychological 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. Abuse has been reported in poly-drug

abusers. Rivotril should be used with extreme caution in patients with a history of alcohol 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, diarrhea, muscle pain, extreme anxiety, tension, restlessness, mood changes, 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.

2.4.3 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 seriously impaired. This effect is aggravated by consumption of alcohol.
Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. The decision 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 2.4.5 Interactions with other Medicinal Products and other Forms of Interaction and 2.6 Undesirable Effects).

2.4.4 Interactions with other Medicinal Products and other Forms of Interaction

Rivotril can be administered concurrently with one or more antiepileptic agents. The probability of pharmacokinetic interactions with these other drugs is low. Nevertheless, 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, lamotrigine, and to a lesser extent valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter by up to 38% during combined treatment.
Rivotril has the potential to influence concentrations of phenytoin. Due to the bi-directional nature of the clonazepam-phenytoin interaction, phenytoin levels have been found to be unchanged, increased or decreased upon coadministration with Rivotril depending on dosing and patient factors.
Rivotril itself does not induce the enzymes responsible for its own metabolism. The enzymes involved in the metabolism of Rivotril have not been clearly identified but include CYP3A4. Inhibitors of CYP3A4 (e.g., fluconazole) may impair the metabolism of Rivotril and lead to exaggerated concentrations and effects.
The selective serotonin uptake inhibitors sertraline (weak CYP3A4 inducers), fluoxetine (CYP2D6 inhibitor) and the anti-epileptic drug felbamate (CYP2C19 inhibitor; CYP3A4 inducer) do not affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic Drug-Drug Interactions (DDI)

The combination of Rivotril with valproic acid may occasionally cause petit mal status epilepticus.
Enhanced side effects such as sedation and cardio-respiratory depression, may also 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.
Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see 2.4 Warnings and Precautions).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

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. It should be borne in mind that both pregnancy itself and abrupt discontinuation of the medication can cause exacerbation of epilepsy.
Withdrawal symptoms in newborn infants have occasionally been reported with benzodiazepines.

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, breast-feeding 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 airway. See 2.4.1 General (Warnings and Precautions).

2.5.5 Geriatric Use

Benzodiazepine pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function.

2.5.6 Renal Impairment

See 3.2.5 Pharmacokinetics in Special Populations

2.5.7 Hepatic Impairment

See 2.2.1 Special Dosage Instruction and 2.4.1 General (Warnings and Precautions).

2.6 Undesirable Effects

2.6.1 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: emotional and mood disturbances, 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: restlessness, irritability, aggressiveness, agitation, nervousness, hostility, anxiety, sleep disturbances, delusion, anger, nightmares and abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur.
Should this occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.
In rare cases changes in libido may occur.
Dependence and withdrawal, see section 2.4.2 Drug Abuse and Dependence.
Nervous system Disorders: impaired concentration, 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 Connective 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, apnoea, 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. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (See 3.2.1 Pharmacokinetic properties; Absorption). 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. The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

There are also animal data showing an effect of clonazepam on serotonin. Animal data and electroencephalographic 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 of Rivotril tablets. Peak plasma concentrations of clonazepam are reached in 1-4 hours. The absorption half –life is around 25 mins. The absolute bioavailability is around 90% with large differences between individuals.

Rivotril tablets are bioequivalent to an oral solution with respect to the extent to clonazepam absorption, whereas the rate of absorption is slightly slower for the tablets.

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. Severe toxic effects including increased frequency of seizures developed in the majority of patients with steady state plasma concentrations above 100 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 or weakly active 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 and is independent of the dose. The clearance is close to 55 ml/min irrespective of gender, but weight-normalized values declined with increasing body weight. 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.

3.2.5 Pharmacokinetics in Special Populations

Renal Impairment

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

Hepatic Impairment

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

Although the influence of hepatic impairment on clonazepam pharmacokinetics has not been further investigated. Experience with another closely related nitrobenzodiazepine (nitrazepam) indicates that clearance of unbound clonazepam might be reduced in liver cirrhosis.

Elderly Patients:

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

Pediatric Patients:

Overall the elimination kinetics in children are similar to those observed in adults. After therapeutic doses to children (0.03-0.11 mg/kg) the serum concentrations were in the same range (13-72 ng/ml) as effective concentrations in adults.

In neonates 0.10 mg/kg doses led to concentrations between 28-117 ng/ml at the end of a short infusion, dropping to 18 – 60 ng/ml 30 minutes later; these were tolerated with no appreciable side effects. In neonates clearance values are dependent on post-natal age. Elimination half-life values in neonates are of the same magnitude as those reported in adults.

In children clearance values of 0.42+/- 0.32 ml/min/kg (ages 2-18 years) and 0.88 +/- 0.4 ml/min/kg (ages 7-12 years) were reported; these values decreased with increasing body weight. Ketogenic diet in children does not affect clonazepam concentrations.

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-foetal 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 Pregnancy).

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

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

Some dosage forms of Rivotril are sensitive to light, therefore caution should be taken regarding storage.

Tablets in blister: keep blister in the outer carton in order to protect from light.

Do not store above 30 °C.

4.2 Packs

Tablets (scored) 0.5 mg	60
Tablets (scored) 2 mg	60

Medicine: keep out of reach of children

MYRivotril0119/CDS7.2

Made for F. Hoffmann-La Roche Ltd,
Basel, Switzerland
by Recipharm Leganés S.L.U.
Leganés, Spain