Rivotril®

PHYSICIAN'S PRESCRIBING INFORMATION

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.**
- **The use of benzodiazepines, including Rivotril, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing Rivotril and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.**
- **The continued use of benzodiazepines, including Rivotril, may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of Rivotril after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue Rivotril or reduce the dosage.**

1. NAME OF THE MEDICINAL PRODUCT

Rivotril

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rivotril oral liquid contains 2.5 mg/mL clonazepam (one drop contains 0.1 mg clonazepam).

Excipients with known effect

Contains saccharin.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Rivotril 2.5 mg/mL oral liquid is a clear blue homogeneous liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anti-epileptic.
Panic Disorder.

4.2 Posology and method of administration

WARNING: Rivotril Oral liquid
Measure the prescribed dose of Rivotril oral liquid as drops only. Do not administer drops directly into the mouth from the bottle.
After each administration, ensure that the dropper is secure in the neck of the bottle.
Drops should be given with a spoon.
After each opening, make sure the dropper is secured within the neck of the bottle.

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.

Discontinuation or Dosage Reduction of Rivotril:
To reduce the risk of withdrawal reactions, increased seizure frequency, and status epilepticus, use a gradual taper to discontinue Rivotril or reduce the dosage. If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level. Subsequently decrease the dosage more slowly.

Caution
Do not administer drops directly into the mouth from the bottle.
After each administration, ensure that the dropper is secure in the neck of the bottle.
Drops should be given with a spoon.
Clonazepam is compatible with water, tea or fruit juice.

Special Populations
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 5.2 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 4.4 Special Warnings and Precautions for Use).

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 4.8 Undesirable Effects).

Panic disorder

Pediatric Patients

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

4.3 Contraindications

Rivotril is contraindicated in patients with a known hypersensitivity to benzodiazepines or any of the excipients of Rivotril listed in section 6.1.

Rivotril is contraindicated in patients with chronic obstructive airways disease with incipient respiratory failure; severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy; dependence on drugs of abuse and CNS depressants including alcohol.

4.4 Special warnings and precautions for use

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

Use in Hepatic impairment

Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment (see section 4.3 Contraindications). Special caution should be exercised when administering Rivotril to patients with mild to moderate hepatic impairment. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic liver function tests are recommended.

Following the prolonged use of Rivotril at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from 4 weeks to 4 months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of Rivotril (see section 4.4 Special warnings and precautions for use, Dependence).

Only a small minority of patients with the common seizure types achieves a lasting remission with clonazepam. Tolerance to the anticonvulsant effect of clonazepam may occur after 4 weeks to 6 months of continuous treatment in the majority of patients leading to increased seizure frequency. Increasing the dose in this situation is rarely worthwhile. If seizures are no longer being adequately controlled, the medicine should be discontinued and alternative treatment implemented.

Porphyria

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

Concomitant use of alcohol and CNS depressants

The concomitant use of Rivotril with alcohol and/or CNS depressants 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 cardiovascular depression (see section 4.5 Interactions with other medicines and other forms of interactions and section 4.9 Overdose).

Since alcohol can provoke epileptic seizures irrespective of therapy and may potentiate the CNS depressant effects of clonazepam, it is imperative that patients should abstain from drinking alcohol while under treatment with Rivotril. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of Rivotril.

Rivotril should be used with particular care in patients with ataxia, in the event of acute intoxication with alcohol or drugs, other anti-epileptic medicines, hypnotics, analgesics, neuroleptic agents, antidepressants or lithium, or if the patient suffers from sleep apnoea.

As up to 70% of clonazepam metabolites are excreted via the kidneys, the pharmacodynamics of clonazepam and its metabolites might be altered.

Hypotension

Although hypotension has occurred rarely, Rivotril should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines. The risk increases at higher doses.

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.

Myasthenia gravis

As with any substance with CNS depressant and / or muscle relaxant properties, Rivotril could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Acute narrow-angle glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired renal function and blood dyscrasias

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances patients on benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. In patients in whom benzodiazepine therapy for periods longer than 4 weeks is deemed necessary, periodic blood counts are recommended.

Psychiatric and Paradoxical Reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, nervousness, hostility, anxiety, delusion, sleep disturbances, nightmares, hallucinations, psychoses, vivid dreams, acute rage, stimulation or excitement, inappropriate behaviour and other adverse behavioural effects may occur. Should such reactions occur, Rivotril should be discontinued.

Impaired Respiratory Function

Caution in the use of Rivotril is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease (COPD), benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension. The dosage of Rivotril must be carefully adjusted to individual requirements in patients with pre-existing disease of the respiratory system.

Depression, Psychosis and Schizophrenia

Rivotril is not recommended as primary therapy in patients with depression and/or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required. Patients with a history of depression and/ or suicide attempts should be kept under close supervision.

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 section 4.5 Interactions with other medicines and other forms of interactions).

When Rivotril is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures. When in the judgement of the clinician, the need for dosage reduction or discontinuation arises, this should be done gradually.

Abuse

Caution must be exercised in administering Rivotril to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence

The use of benzodiazepines may lead to development of physical and psychological dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the medicine. 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 users. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms range from insomnia, anxiety, agitation, sleep disturbances, headaches, diarrhoea, irritability, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short-term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, Rivotril should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 – 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Following the short-term treatment of patients with panic disorder in Studies 1 and 2 (see section 5.1- Pharmacodynamic Propreties - Clinical Trials), patients were gradually withdrawn during a 7-week downward-titration (discontinuance) period. Overall, the discontinuance period was associated with good tolerability and a very modest clinical deterioration, without evidence of a significant rebound phenomenon. However, there are not sufficient data from adequate and well-controlled long-term clonazepam studies in patients with panic disorder to accurately estimate the risks of withdrawal symptoms and dependence that may be associated with such use.

Use in the Elderly

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.

Elderly or debilitated patients may be particularly susceptible to the pharmacologic effects of benzodiazepines such as giddiness, ataxia and confusion, which may increase the risk of a fall. Literature suggests that such 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.

Elderly patients, patients with pre-existing disease of the respiratory system (e.g. chronic obstructive lung disease), liver or kidney disease, or those who are receiving treatment with other centrally acting medications or anticonvulsant agents, require very careful dosage adjustment.

Paediatric Use

Salivary and bronchial hypersecretion can occur in infants and small children and supervision is required to ensure that airways remain free, especially on commencing therapy or in the event of respiratory infection.

Safety and effectiveness in paediatric patients with panic disorder below the age of 18 have not been established.

Effects on laboratory tests

No data available.

4.5 Interaction with other medicinal products and other forms of interaction

Rivotril can be administered concurrently with one or more other anti-epileptic medicines, in which case the dosage of each medicine must be adjusted to achieve the optimum effect. Interactions have been reported between some benzodiazepines and other anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the other anticonvulsant is performed more frequently.

Pharmacokinetic Interactions

The anti-epileptic medicines phenytoin, phenobarbitone, carbamazepine, lamotrigine and valproate may increase the clearance of clonazepam, thereby decreasing the plasma concentrations of the latter during combined treatment.

Phenytoin

The effect of clonazepam on phenytoin plasma levels is not clear as the latter may increase or decrease according to study reports depending on dosing and patient factors.

Carbamazepine

Levels may be lowered by clonazepam.Rivotril itself does not appear to 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 reuptake inhibitors (SSRIs) sertraline and fluoxetine do not significantly affect the pharmacokinetics of clonazepam when administered concomitantly.

Pharmacodynamic Interactions
Benzodiazepines, including Rivotril, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g. other anticonvulsant (anti-epileptic) agents, lithium, barbiturates, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics. This is especially true in the presence of alcohol (see section 4.4 Special warnings and precautions for use).

Rivotril undergoes oxidative metabolism and, consequently, may interact with disulfiram or cimetidine resulting in increased plasma levels of Rivotril. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

The anticholinergic effects of atropine and similar medicines, antihistamines and antidepressants may be potentiated.
Minor EEG changes, usually low voltage fast activity, of no known clinical significance, has been reported with benzodiazepine administration.
Some specific interactions noted with clonazepam are:

Alcohol

Epileptic patients should 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 (see section 4.4 Special warnings and precautions for use).

Sodium valproate - reports of sodium valproate causing petit mal status epilepticus with clonazepam exist.

4.6 Fertility, pregnancy and lactation

Effects on Fertility
Dietary administration of clonazepam to male and female rats was associated with a reduced pregnancy rate and impaired pup survival at doses of 60 mg/m^2/day or greater (4-fold the maximal recommended human dose [MRHD]); the no effect dose was 6 mg/m^2/day (less than clinical exposure).

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day, there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning. The lowest dose tested is approximately 5 and 24 times the maximum recommended human dose (MRHD) of 20 mg/day for seizure disorders and 4 mg/day for panic disorder, respectively, on a body surface area (mg/m^2) basis.

Use in Pregnancy
The risk of a mother with epilepsy giving birth to a baby with an abnormality is about three times that of the normal population. Some of this risk is due to the anticonvulsant medicines taken. Mothers taking more than one anticonvulsant medicine might have a higher risk of having a baby with a malformation than mothers taking one medicine.

Overall the risk of having an abnormal child is far outweighed by the dangers to the mother and foetus of uncontrolled convulsions. It is therefore recommended that:
women on anticonvulsant medicines receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;anticonvulsant should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose;

folic acid supplement (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;

specialist prenatal diagnosis including detailed midtrimester ultrasound should be offered.

Clonazepam is a benzodiazepine. These medicines cross the placenta and appear in the foetus and may, after continuous administration during a large part of pregnancy, give rise to irregularities in the heartbeat of the unborn child, hypotonia, reduced respiratory function, poor feeding and hypothermia in the newborn child. Withdrawal symptoms in newborn infants have occasionally been reported with this class of medicines.

Oral administration of clonazepam during the period of organogenesis has elicited a low, nondose-related incidence of a similar pattern of malformations in rabbits (cleft palate, open eyelids, fused sternebrae, limb defects) and mice (exencephaly, central nervous system defects) at doses less than MRHD. These effects were not observed in rats at oral doses more than 20-fold MRHD. The clinical significance of these findings is unknown.

The lowest dose tested is less than the maximum recommended human dose (MRHD) of 20 mg/day for seizure disorders and similar to the MRHD of 4 mg/day for panic disorder, on a mg/m^2 basis. Reductions in maternal weight gain occurred at doses of 5 mg/kg/day or greater and reduction in embryofetal growth occurred in one study at a dose of 10 mg/kg/day.

No adverse maternal or embryofetal effects were observed in mice or rats following oral administration of clonazepam during organogenesis of doses up to 15 or 40 mg/kg/day, respectively (4 and 20 times the MRHD of 20 mg/day for seizure disorders and 20 and 100 times the MRHD of 4 mg/day for panic disorder, respectively, on a mg/m^2 basis).

Withdrawal symptoms in newborn infants have been reported with benzodiazepines.

Use in Lactation
Rivotril must not be given to nursing women. Rivotril is excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant. If there is a compelling reason for use, breastfeeding should be discontinued.

4.7 Effects on ability to drive and use machines

As with all patients taking CNS-depressant medications, patients receiving Rivotril should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not

become drowsy or dizzy from Rivotril therapy. Abilities may be impaired on the day following use (see section 4.5 Interactions with other medicines and other forms of interactions).

4.8 A dverse effects (Undesirable effects)

4.8.1 Clinical Trials

The adverse effects for Rivotril are provided separately for patients with seizure disorders and with panic disorder.

Seizure Disorders

Adverse effects to Rivotril occur in about 50% of patients, depending on dose and are usually referable to its sedative and muscle relaxant effects and are also usually transitory (however, they can continue in up to 10% of patients and may result in withdrawal of the medicine). Adverse effects can, to a certain extent, be avoided by a low initial dose which is gradually increased in the absence of side effects.

Adverse events which have been reported and may be related to clonazepam administration are

Cardiac Disorders: palpitations;

Endocrine Disorders: Increased libido, hirsutism.

Gastrointestinal Disorders:

Anorexia, vomiting, dyspepsia, increased appetite, constipation, dysphagia, hyperphagia, hepatomegaly.

General Disorders and Administration Site Conditions:

Ankle and facial oedema, lethargy.

Haemic and Lymphatic System Disorders:

Leucopenia, eosinophilia, anaemia, lymphadenopathy.

Investigations:

Abnormal liver function test;

Metabolism and Nutrition Disorders:

Weight gain, weight loss, dehydration.

Nervous System Disorders:

Apathy, aphonia, coma, dysdiadochokinesis (inability to perform rapid, alternating movements), hemiparesis, respiratory depression, tremo.

Psychiatric Disorders:

Dysphoria, forgetfulness, hallucinations, hysteria, insomnia, psychosis, suicidal attempt (the behavioural effects are more likely to occur in patients with a history of psychiatric disturbances);

Renal and Urinary Disorders:

Dysuria, enuresis, nocturia, urinary retention.

Respiratory Thoracic and Mediastinal System Disorders:

Chest congestion, mucus obstruction of nasopharynx, rhinorrhoea, shortness of breath.

Panic Disorder

Adverse events during exposure to Rivotril were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:

Adverse Events Associated with Discontinuation of Treatment:

Overall, the incidence of discontinuation due to adverse events was 17% in Rivotril compared to 9% for placebo in the combined data of two 6- to 9-week trials. The most common events (≥1%) associated with discontinuation and a dropout rate twice or greater for Rivotril than that of placebo included the following:

Table 1 Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment

Adverse Event	Rivotril (N=574)	Placebo (N=294)
Somnolence	7%	1%
Depression	4%	1%
Dizziness	1%	<1%
Nervousness	1%	0%
Ataxia	1%	0%
Intellectual Ability Reduced	1%	0%

Adverse Events Occurring at an Incidence of 1% or More among Rivotril-Treated Patients:

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6- to 9-week trials. Events reported in 1% or more of patients treated with Rivotril (doses ranging from 0.5 to 4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in Table 2 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide

the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 2 Treatment-Emergent Adverse Event Incidence in 6- to 9-Week Placebo-Controlled Clinical Trials*

	Clonazepam Maximum Daily Dose					
Adverse Event by Body System	**<1mg n=96 %**	**1-<2mg n=129 %**	**2-<3mg n=113 %**	**≥3mg n=235 %**	**All Rivotril Groups N=574 %**	**Placebo N=294 %**
Central & Peripheral Nervous System						
Somnolence†	26	35	50	36	37	10
Dizziness	5	5	12	8	8	4
Coordination Abnormal†	1	2	7	9	6	0
Ataxia†	2	1	8	8	5	0
Dysarthria†	0	0	4	3	2	0
Psychiatric						
Depression	7	6	8	8	7	1
Memory Disturbance	2	5	2	5	4	2
Nervousness	1	4	3	4	3	2
Intellectual Ability Reduced	0	2	4	3	2	0
Emotional Lability	0	1	2	2	1	1
Libido Decreased	0	1	3	1	1	0
Confusion	0	2	2	1	1	0
Respiratory System						
Upper Respiratory Tract Infection†	10	10	7	6	8	4
Sinusitis	4	2	8	4	4	3
Rhinitis	3	2	4	2	2	1
Coughing	2	2	4	0	2	0
Pharyngitis	1	1	3	2	2	1
Bronchitis	1	0	2	2	1	1
Gastrointestinal System						
Constipation†	0	1	5	3	2	2
Appetite Decreased	1	1	0	3	1	1
Abdominal Pain†	2	2	2	0	1	1
Body as a Whole						
Fatigue	9	6	7	7	7	4
Allergic Reaction	3	1	4	2	2	1
Musculoskeletal						
Myalgia	2	1	4	0	1	1
Resistance Mechanism Disorders						
Influenza	3	2	5	5	4	3
Urinary System						
Micturition Frequency	1	2	2	1	1	0
Urinary Tract Infection†	0	0	2	2	1	0

Clonazepam Maximum Daily Dose						
Adverse Event by Body System	**<1mg n=96 %**	**1-<2mg n=129 %**	**2-<3mg n=113 %**	**≥3mg n=235 %**	**All Rivotril Groups N=574 %**	**Placebo N=294 %**
Vision Disorders						
Blurred Vision	1	2	3	0	1	1
Reproductive Disorders‡						
Female						
Dysmenorrhea	0	6	5	2	3	2
Colpitis	4	0	2	1	1	1
Male						
Ejaculation Delayed	0	0	2	2	1	0
Impotence	3	0	2	1	1	0

* Events reported by at least 1% of patients treated with Rivotril and for which the incidence was greater than that for placebo.

† Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was ≤0.10.

‡ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.

Commonly Observed Adverse Events:

Table 3 Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9-Week Trials

Adverse Event	Clonazepam (N=574)	Placebo (N=294)
Somnolence	37%	10%
Depression	7%	1%
Coordination Abnormal	6%	0%
Ataxia	5%	0%

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

Treatment-Emergent Depressive Symptoms:

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term "depression" were reported in 7% of Rivotril-treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same trials, adverse events classified under the preferred term "depression" were reported as leading to discontinuation in 4% of Rivotril-treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam-treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of Rivotril in Panic Disorder:

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with Rivotril at multiple doses during clinical trials. All reported events are included except those already listed in Table 2 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with Rivotril, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural

Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: thirst, gout

Musculoskeletal System Disorders: back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased, aggression, apathy, disturbance in attention, excitement, anger, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity

Reproductive Disorders, Male: ejaculation decreased

Resistance Mechanism Disorders: infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy

Skin and Appendages Disorders: acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder

Special Senses Other, Disorders: taste loss

Urinary System Disorders: dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration

Vascular (Extracardiac) Disorders: thrombophlebitis leg

Vision Disorders: eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

4.8.2 Post-Marketing Experience

Cardiac disorders:

Cardiac failure including cardiac arrest has been reported.

Endocrine disorders:
Isolated cases of reversible development of premature secondary sex characteristics in children (incomplete precocious puberty) have been reported.
Eye Disorders: Particularly in long-term or high-dose treatment, reversible disorders of vision (diplopia) may occur.

Gastrointestinal disorders:

Hypersalivation occurs relatively commonly. The following effects have been reported in rare cases: nausea and epigastric symptoms (discomfort).

General disorders and administration site conditions:

Fatigue (tiredness, lassitude) occurs relatively frequently and is usually transient and generally disappears spontaneously during 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.

Fever may occur.

In rare cases chest pain or headache may occur.Paradoxical reactions including irritability have been observed (see also Psychiatric disorders).

Haemic and lymphatic system disorders:

In rare cases thrombocytopenia may occur.

Immune system disorders:

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

Musculoskeletal and connective tissue disorders:

Muscle weakness occurs relatively frequently, is usually transient and generally disappears spontaneously during 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.

Nervous system disorders: Impaired concentration, drowsiness, somnolence, slowed reaction, muscular hypotonia, dizziness, ataxia. These undesirable effects occur relatively frequently, are usually transient and generally disappear spontaneously during 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.

Vertigo occurs relatively commonly.

Particularly when treatment is over prolonged periods or at high doses, reversible disorders such as a slowing or slurring of speech (dysarthria), reduced coordination of gait and movements (ataxia) or nystagmus may occur.

Anterograde amnesia may occur with the use of benzodiazepines 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 is possible.

Psychiatric disorders:

Emotional and mood disturbances, confusional state and 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, abnormal dreams, hallucinations, psychoses, hyper activity, inappropriate behaviour and other adverse behavioural effects are known to occur. Should this occur, the use of the drug should be discontinued.

In rare cases loss and /or changes in libido may occur.

Dependence and withdrawal (see section 4.4 Special warnings and precautions for use).

Renal and urinary disorder:

In rare cases urinary incontinence may occur.

Reproductive system and breast disorder:

In rare cases erectile dysfunction may occur.

Respiratory, thoracic and mediastinal ystem disorders:

Bronchial hypersecretion occurs relatively commonly. Pharyngeal oedema has been reported in rare cases. Respiratory depression is possible. Depression of respiration may be increased if there is obstruction of the airways or pre-existing brain damage, or if other medications, which depress respiration, have been given. This effect can be avoided by careful adjustment of the final dose.

In infants and young children, Rivotril may cause increased production of saliva and bronchial secretions; therefore, special attention must be paid to maintaining patency of the airways.

Skin and subcutaneous tissue disorders:

The following effects may occur in rare cases: urticaria, pruritus, skin rash, transient hair loss (alopecia), angioneurotic oedema, pigmentation disorder.

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.

Reporting of suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the national regulation by using the form http://sideeffects.health.gov.il

4.9 Overdose

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, dysarthria, nystagmus, hypotonia, hypotension, respiratory depression, coma and very rarely, death. Coma may be more protracted and cyclical, particularly in elderly patients. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (see section 5.2 Pharmacokinetic properties). Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1-2 hours, consider activated charcoal with airway protection if indicated.

If CNS depression is severe consider the use of flumazenil, 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 may precipitate seizures and is to be used with extreme caution in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to the prescribing information for flumazenil, for further information on the correct use of this medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic agent, antipanic agent. ATC code: N03AE01.

Mechanism of action

Clonazepam is an anticonvulsant which exhibits several pharmacological properties characteristic of the benzodiazepine class of medicines.

The exact site and mode of action of the anticonvulsant action of clonazepam is unknown.

Benzodiazepines enhance the polysynaptic inhibitory processes at all levels of the central nervous system. Clonazepam is more effective in blocking spread of electrical activity in the lesion itself.

Antipanic: The precise mechanism by which clonazepam exerts its antipanic effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system.

Clinical trials

Seizure Disorders: No data available.

Panic Disorder: The effectiveness of Rivotril in the treatment of panic disorder was demonstrated in two double-blind, placebo-controlled studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IIIR) with or without agoraphobia. In these studies, Rivotril was shown to be significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency, the Clinician's Global Impression Severity of Illness Score and the Clinician's Global Impression Improvement Score.

Study 1 was a 9-week, fixed-dose study involving Rivotril doses of 0.5, 1, 2, 3 or 4 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose, and a 7-week discontinuance phase. A significant difference from placebo was observed consistently only for the 1 mg/day group. The difference between the 1 mg dose group and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

Study 2 was a 6-week, flexible-dose study involving Rivotril in a dose range of 0.5 to 4 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a 6-week optimal-dose, and a 6-week discontinuance phase. The mean clonazepam dose during the optimal dosing period was 2.3 mg/day. The difference between Rivotril and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

5.2 Pharmacokinetic properties

Absorption

Clonazepam is rapidly and almost completely (82 - 98%) absorbed after oral administration of Rivotril tablets, with peak serum levels being reached between 2 - 3 hours. The absorption half-life is 24 min. Rivotril tablets are similar to an oral solution with respect to the extent of clonazepam absorption, whereas the rate of absorption is different (slightly slower for the tablets). With continuous therapy, accumulation occurs and although values differ in

different reports, the therapeutic serum level appears to be between 10 and 80 n-anogram/mL. In one study with increase in dosage to 5 mg/day the average level of clonazepam after 15 days was 54 nanogram/mL. A steady state is usually reached within 2 - 3 weeks.

Plasma concentrations of clonazepam at steady states for once daily dosage regimens are 3-fold higher than those after single oral doses. Following multiple oral doses of 2 mg three times daily steady-state pre-dose plasma concentrations of clonazepam ranged from 30 - 80 nanogram/mL. The plasma concentration-dose relationship of clonazepam is linear. Severe toxic effects, resulting in increased frequency of seizures for some patients, have been reported at steady state plasma concentrations above 100 nanogram/mL.

The absolute bioavailability is 90%.

Distribution

Clonazepam enters the cerebral tissues rapidly.The distribution half-life is approximately between 0.5- 1 hours. The apparent volume of distribution, 3 L/kg, suggests concentration in some tissues.

The plasma protein binding of clonazepam ranges from 82-86%.

Metabolism

Clonazepam is metabolised in the liver. The metabolic pathways include hydroxylation, reduction of the nitro groups to an amine and addition of acetate to the amino grouping. Clonazepam is extensively metabolised by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamido-clonazepam. Hydroxylation at the C-3 position also occurs. Hepatic cytochrome P450 3A4 is implicated in the nitroreduction of clonazepam to pharmacologically inactive metabolites.

Excretion

The mean elimination half-life is 39.0 ± 8.3 hours.

50- 70% of the dose is excreted in the urine and 10- 30% in the 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.

Clinical significance of pharmacokinetics

With chronic dosing, accumulation occurs. However, there is a wide variation in therapeutic plasma levels and a correlation between adverse effects with plasma levels or the rate of increase in plasma concentration of clonazepam and its metabolites has not been established. Consequently, monitoring of plasma levels, as is often done with some anticonvulsants, would be valuable.

It should be emphasised that because of the effect of clonazepam on plasma levels of other anticonvulsants administered concomitantly (and vice versa) the patient should be monitored carefully in the initial stages for clinical response and occurrence of side effects.

Pharmacokinetics in Special Populations

Renal Impairment

Renal impairment does not affect the pharmacokinetics of clonazepam. Therefore, based on pharmacokinetic considerations, no dosage adjustment may be required in patients with renal

impairment. The pharmacodynamics of probable accumulated clonazepam metabolites may necessitate dosage review in these patients.

Hepatic Impairment
The influence of hepatic disease on clonazepam pharmacokinetics has not been investigated. However, due to the sole hepatic metabolism of clonazepam, the pharmacokinetics of clonazepam are expected to be affected on theoretical grounds.

Elderly Patients
The pharmacokinetics of clonazepam in the elderly has not been established.

Neonates
Although the elimination half-life (41.9 ± 29.8 hours) and clearance values in neonates pre-treated with phenobarbital are the same order of magnitude as those reported in non-pretreated adults, postnatal age does, however, affect the clearance of clonazepam under normal conditions.

5.3 Preclinical safety data

Genotoxicity
Clonazepam and five of its metabolites were negative in bacterial gene mutation assays. Chromosomal damage assays have not been conducted with clonazepam.

Carcinogenicity
No 2-year carcinogenicity studies have been conducted with clonazepam. An 18-month chronic study in rats showed no treatment-related histopathological changes at dietary doses up to 1800 mg/m^2/day (greater than 100-fold MRHD).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients *Rivotril oral liquid*
Peach flavouring, saccharin sodium, brilliant blue FCF, glacial acetic acid, propylene glycol.

6.2 Shelf life
The expiry date of the product is indicated on the packaging materials.

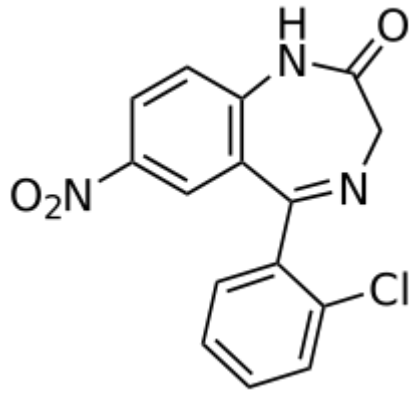
6.3 Special precautions for storage
Store below 25°C.
Once the bottle has been opened, Rivotril drops are stable for 120 days.

6.4 Nature and contents of container
Rivotril 2.5 mg/mL oral liquid is supplied in a 10 mL coloured glass type III glass bottles with a child resistant HDPE closure and a controlled release LDPE dropper.

6.5 Special precautions for disposal and other handling
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

6.6 Physiochemical properties
Chemical structure

Clonazepam has the following chemical structure,(5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4 benzodiazepin-2-one) and a molecular weight 315.7:



CAS number

1622-61-3

7. MARKETING AUTHORISATION HOLDER

Tzamal Bio-pharma Ltd., 20 Hamagshimim st., Petach-Tikva

8. MARKETING AUTHORISATION NUMBER

061-31-21476-00

9. MANUFACTURER

CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany

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