PRODUCT MONOGRAPH

# RIVOTRIL®

clonazepam

0.5 mg and 2 mg Tablets

Anticonvulsant

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**RIVOTRIL®**
clonazepam

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablet 0.5 mg | cornstarch, iron oxide red, iron oxide yellow, lactose, magnesium stearate, potato starch and talc |
| Oral | Tablet 2 mg | cornstarch, lactose, magnesium stearate and microcrystalline cellulose |

### INDICATIONS AND CLINICAL USE

RIVOTRIL (clonazepam) has been found useful when used alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome).

RIVOTRIL may be of some value in patients with absence spells (petit mal) who have failed to respond to succinimides.

Up to nearly one-third of the patients in some studies have shown a loss of anticonvulsant activity, often within the first three months of administration of RIVOTRIL. In some cases dosage adjustment may re-establish efficacy.

**Geriatrics** (>65 years of age)
In general elderly patients should be started on lowest possible dose of RIVOTRIL and observed closely. Long-term use of RIVOTRIL should be avoided in elderly patients. Enhanced monitoring is recommended (see WARNINGS AND PRECAUTIONS, Falls and fractures; Special Populations and DOSAGE AND ADMINISTRATION, Dosing considerations).

**Pediatrics** (<18 years of age)
For a brief description see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (<5 years of age) and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Children.

## CONTRAINDICATIONS

- Patients who are hypersensitive to other benzodiazepines, this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph
- Severe respiratory insufficiency
- Severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy.
- Sleep apnea syndrome
- Myasthenia gravis
- Narrow angle glaucoma

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Addiction, Abuse and Misuse**
The use of benzodiazepines, including RIVOTRIL, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing RIVOTRIL
- Monitor all patients regularly for the development of these behaviours or conditions.
- RIVOTRIL should be stored securely to avoid theft or misuse.

**Withdrawal**
Benzodiazepines, like RIVOTRIL, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of RIVOTRIL.
- Terminate treatment with RIVOTRIL by gradually tapering the dosage schedule under close monitoring.

(see WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

**Risks from Concomitant use with Opioids**
Concomitant use of RIVOTRIL and opioids may result in profound sedation, respiratory depression, coma and death (see WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

**General**

A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with RIVOTRIL (clonazepam). When used in patients in whom several different types of seizures coexist, RIVOTRIL may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). These phenomena may require the addition of appropriate anticonvulsants or an increase in their dosage. The concomitant use of valproic acid and clonazepam may produce absence status.

The abrupt withdrawal of RIVOTRIL, particularly in those patients on long-term, high dose therapy, may precipitate status epilepticus. Therefore, as with any other anticonvulsant, gradual withdrawal is essential when discontinuing RIVOTRIL. While RIVOTRIL is being gradually withdrawn, the simultaneous substitution of incremental doses of another anticonvulsant may be indicated.

**Concomitant use with opioids:** Concomitant use of benzodiazepines, including RIVOTRIL, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; DRUG INTERACTIONS, Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe RIVOTRIL concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of RIVOTRIL than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking RIVOTRIL, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see OVERDOSAGE).

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.

**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 CONTRAINDICATIONS).

**CNS, psychosis and depression**

Rivotril should be used with particular caution in patients with ataxia.

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

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

**Concomitant use of alcohol/CNS depressants**

The concomitant use of RIVOTRIL with alcohol and/or 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 cardiovascular depression (see DRUG INTERACTIONS and OVERDOSAGE).

RIVOTRIL should be used only with particular caution in patients with ataxia, and in the event of acute intoxication with alcohol or drugs.
Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

**Psychiatric and 'paradoxical' reactions**

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, anxiety, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

**Psychiatric**

**Suicidal Ideation and Behaviour:**

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications.

Patients with a history of depression and/or suicide attempts should be kept under close supervision. All patients treated with antiepileptic drugs (AEDs), irrespective of indication, should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

An FDA meta-analysis of randomized placebo controlled trials, in which AEDs were used for various indications, has shown a small increased risk of suicidal ideation and behaviour in patients treated with these drugs. The mechanism of this risk is not known. There were 43,892 patients treated in the placebo controlled clinical trials that were included in the meta-analysis. Approximately 75% of patients in these clinical trials were treated for indications other than epilepsy and, for the majority of non-epilepsy indications the treatment (AED or placebo) was administered as monotherapy. Patients with epilepsy represented approximately 25% of the total number of patients treated in the placebo controlled clinical trials and, for the majority of epilepsy patients, treatment (AED or placebo) was administered as adjunct to other antiepileptic agents (i.e., patients in both treatment arms were being treated with one or more AEDs). Therefore, the small increased risk of suicidal ideation and behaviour reported from the meta-analysis (0.43% for patients on AEDs compared to 0.24% for patients on placebo) is based largely on patients that received monotherapy treatment (AED or placebo) for non-epilepsy indications. The study design does not allow an estimation of the risk of suicidal ideation and

behaviour for patients with epilepsy that are taking AEDs, due both to this population being the minority in the study, and the drug-placebo comparison in this population being confounded by the presence of adjunct AED treatment in both arms.

**Amnesia**

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

**Lactose intolerance**
Lactose is a non-medicinal ingredient in RIVOTRIL. Therefore, 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.

**Medical history of alcohol or drug abuse**
RIVOTRIL should be used with extreme caution in patients with a history of alcohol or drug abuse. Benzodiazepines have produced habituation, dependence and withdrawal symptoms similar to those noted with barbiturates and alcohol. The risk of dependence increases with dose and duration, and is greater in patients with a medical history of alcohol and drug abuse (See WARNINGS AND PRECAUTIONS, Dependence and Tolerance).

**Dependence and Tolerance**
Use of benzodiazepines, such as RIVOTRIL, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with RIVOTRIL with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing RIVOTRIL. In individuals prone to substance use disorder, RIVOTRIL should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- RIVOTRIL should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

**Withdrawal**
Benzodiazepines, such as RIVOTRIL, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

(see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; DOSAGE AND ADMINISTRATION, Dosing Considerations)

**Driving and Hazardous Activities**
Patients receiving RIVOTRIL should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle. Sedation, amnesia and impaired muscular function are effects of benzodiazpines that can adversely affect the ability to drive or operate machinery. This effect is increased if the patient has had alcohol.

Driving, operating machinery and other hazardous activities should 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 DRUG

INTERACTIONS). They also should be warned against the concomitant use of alcohol and other CNS depressant drugs.

**Renal**
The safety and efficacy of clonazepam in patients with renal impairment has not been studied.

Clonazepam metabolites are excreted by the kidneys; to avoid excessive accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function (See DOSAGE AND ADMINISTRATION, ACTION AND CLINICAL PHARMACOLOGY).

**Respiratory**
Respiratory depression may occur following administration of RIVOTRIL. This effect may be aggravated by pre-existing airway 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.

Treatment with RIVOTRIL should be instituted with caution in patients with chronic respiratory diseases (See CONTRAINDICATIONS).

Hypersecretion in the upper respiratory passages has at times been a troublesome adverse reaction during RIVOTRIL therapy, especially in small mentally retarded children who ordinarily have difficultly handling secretions. Therefore special attention must be paid to maintaining patency of the airways.

**Falls and fractures**
There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

**Hypersalivation**
RIVOTRIL may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, RIVOTRIL should be used with caution in patients with chronic respiratory diseases.

**Carcinogenesis**
See TOXICOLOGY.

**Special Populations**
**Pregnant Women:**
In a reproductive study in rabbits, administration of clonazepam was associated with an increased incidence of cleft palate and other anomalies at two dose levels (see TOXICOLOGY: Teratogenicity).

Reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased two to three-fold. The increase

is largely due to specific defects, e.g., congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g., genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

The preceding considerations should be borne in mind and clonazepam should be used in women of childbearing potential only when the expected benefits to the patient warrant the possible risk to a fetus. 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. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. Withdrawal symptoms in newborn infants have occasionally been reported with benzodiazepines

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risk of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of childbearing age should be encouraged to seek professional counsel and should report the onset of pregnancy promptly to their physician. Where the necessity for continued use of anti-epileptic medication is in doubt, appropriate consultation might be indicated.

**Pregnancy Registry:**
To provide information regarding the effects of *in utero* exposure to RIVOTRIL, physicians are advised to recommend that pregnant patients taking RIVOTRIL enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website **http://www.aedpregnancyregistry.org/.**

**Nursing Women:** Although the active ingredient of RIVOTRIL has been found to pass into the maternal milk in small amounts only, mothers receiving clonazepam should not breast-feed their infants.

**Pediatrics (< 5 years of age):** Because of the possibility that adverse effects on physical or mental development of the child could become apparent only after years, a risk-benefit consideration of the long-term use of RIVOTRIL is important in paediatric patients.

**Geriatrics:** 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. In general elderly patients should be started on lowest possible dose of RIVOTRIL and observed closely.

There is an increased risk for falls and fractures among elderly and debilitated benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages).

Long-term use of RIVOTRIL should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

**Monitoring and Laboratory Tests**

Periodic liver function tests and blood counts are recommended during long-term therapy with RIVOTRIL.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

**Most Frequent Adverse Reactions:**

The most frequently occurring adverse reactions of RIVOTRIL (clonazepam) are referable to CNS depression. Experience to date has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time. Behaviour problems have been noted in approximately 25% of patients.

Somnolence, slowed reaction, muscular hypotonia, muscle weakness, dizziness, ataxia 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.

**Serious and Important Adverse Reactions:**

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.

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

Release of hostility and other paradoxical effects such as irritability, restlessness, agitation, aggressiveness, delusion, anger, hysteria, rages, nightmares, abnormal dreams, hallucinations, psychoses, hyperactivity, inappropriate behaviour and other adverse behavioural effects are known to occur with the use of benzodiazepines. If these occur, use of the drug should be discontinued. Paradoxical reactions are more likely to occur in children and in the elderly.

Anterograde amnesia may occur with therapeutic doses of benzodiazepines, the risk increasing with higher doses. Effects of anterograde amnesia may be associated with inappropriate behaviour.

Chronic use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (See WARNINGS-and PRECAUTIONS-Dependence and Tolerance).

**Post Market Adverse Drug Reactions**
Other adverse reactions listed by system, are:

***Body as Whole:*** Fever, general deterioration, coated tongue.

***Cardiovascular System:*** Palpitations, cardiac failure including cardiac arrest.

***Dependence/Withdrawal:*** Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as RIVOTRIL. Severe and life-threatening symptoms have been reported. (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

***Digestive System:*** increased salivation, nausea, vomiting, anorexia, constipation, diarrhea, encopresis, dry mouth, increased appetite, abdominal pain, sore gums, gastritis, epigastric symptoms and hepatomegaly.

***Endocrine System:*** gynecomastia, isolated cases of reversible development of premature secondary sexual characteristics in children (incomplete precocious puberty).

***Hemic and Lymphatic System***: Anemia, leukopenia (WBC below 4000/cu mm), decreased platelet count (thrombocytopenia), eosinophilia and lymphadenopathy.

***Injury, Poisoning and Procedural Complications:*** There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

***Metabolic and Nutritional Disorders:*** transient elevations of serum transaminase and alkaline phosphatase, weight gain or loss, dehydration.

***Musculoskeletal System:*** pains such as low back pain.

***Nervous System:*** Abnormal eye movements, nystagmus, dysarthria, vertigo, insomnia, tiredness, lassitude, dysdiadokinesis, aphonia, withdrawal and coma. Isolated reports of akinesia, hemiparesis, slurred speech, tremor, "glassy-eyed" appearance, headache and choreiform movements have been received. Minor changes in EEG patterns, specifically low-voltage fast activity. With certain forms of epilepsy, an increase in the frequency of seizures during long-term treatment is possible. Impaired concentration, restlessness, confusional state, disorientation, depression, paradoxical reactions (excitability, irritability, aggression, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams), increased libido, loss of libido.

***Respiratory System**:* Chest congestion, hypersecretion in the upper respiratory passages, rhinorrhea, shortness of breath, dyspnea and respiratory depression.

***Skin and Appendages**:* nonspecific erythematous, papular and maculopapular skin rashes, swelling of the ankle, face and eyelids (ankle and facial edema), urticaria, pigmentation changes and pruritus. Hirsutism and transient hair loss have also been reported, but drug relationship has not been established.

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

***Urogenital System**:* Rare instances of dysuria, nocturia, urinary incontinence, urinary retention and enuresis.

## DRUG INTERACTIONS

**Serious Drug Interactions**

Concomitant use of RIVOTRIL and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see WARNINGS AND PRECAUTIONS, General, Risks from Concomitant use with Opioids)

### Overview

Simultaneous administration of several anticonvulsant drugs may be considered with RIVOTRIL (clonazepam), however, it should be borne in mind that the use of multiple anti-convulsants may result in an increase of central depressant adverse effects. In addition, the dosage of each drug may be required to be adjusted to obtain the optimal effect.

A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with RIVOTRIL. When used in patients in whom several different types of seizures coexist, RIVOTRIL may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). These phenomena may require the addition of appropriate anticonvulsants or an increase in their dosage. The concomitant use of valproic acid and clonazepam may produce absence status.

Hepatic cytochrome P-450 3A4 is implicated in the metabolism of clonazepam to pharmacologically inactive metabolites. Therefore, concomitant use of drugs that affect the activity of cytochrome P-450 3A4 may alter the pharmacokinetics of clonazepam.

**Drug-Drug Interactions**

***Pharmacokinetic Drug-Drug Interactions (DDI)*:** The antiepileptic drugs phenytoin, phenobarbital, carbamazepine, lamotrigine and valproate may increase the clearance of clonazepam thereby decreasing the plasma concentrations of the latter by upto 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

Clonazepam 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 reuptake inhibitors sertraline (weak CYP3A4 inducer) and fluoxetine (CYP2D6 inhibitor) do not affect the pharmacokinetics of clonazepam when administered concomitantly.

***Pharmacodynamic Drug-Drug Interactions (DDI):***

*CNS–acting drugs*

Epileptic patients being treated with RIVOTRIL must under no circumstances consume alcohol since it may alter the effect of the drug, reduce the efficacy of treatment or produce unwanted effects. 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, narcotics, narcotic analgesics, muscle-relaxants, barbiturates, non-barbiturate hypnotics, anxiolytics/sedatives, antihistamines, phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors, tricyclic antidepressants, and anticonvulsants (see WARNINGS & PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines, Concomitant use of Alcohol/CNS Depressants; OVERDOSAGE).

**Opioids**

Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including RIVOTRIL, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see WARNINGS AND PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines).

In combination therapy with centrally-acting medications, the dosage of each drug must be adjusted to achieve the optimum effect. Because of the potentiation of effects that might occur, patients should be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of clonazepam.

**Drug-Food Interactions**

Interactions with food have not been established. Grapefruit juice decreases the activity of cytochrome P-450 3A4, which is implicated in the metabolism of clonazepam, and may contribute to increased plasma levels of the drug.

**Drug-Herb Interactions**
Interactions with herbal products have not been established.

**Drug-Lifestyle Interactions**
The concomitant use of RIVOTRIL with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of RIVOTRIL possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see WARNINGS AND PRECAUTIONS, Concomitant use of alcohol / CNS depressants).

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

- Dosage of RIVOTRIL (clonazepam) is essentially individual and depends above all on the age of the patient. Dosage must be determined in each patient according to clinical response and tolerance.
- The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be borne in mind whenever RIVOTRIL is added to an already existing anticonvulsant regimen.
- RIVOTRIL should always be prescribed at the lowest effective dose for the shortest duration possible.
- RIVOTRIL can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see WARNINGS AND PRECAUTIONS, Falls and fractures).
- Long-term use of RIVOTRIL should be avoided in elderly patients. Enhanced monitoring is recommended.

### Recommended Dose and Dosage Adjustment

***Children**:* In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day and should not exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.50 mg every third day until a maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase.

***Adults**:* The initial dose for adults should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every three days until seizures are adequately controlled or

until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. A recommended maintenance dose for adults is 8 to 10 mg/day in three divided doses. Dosages in excess of 20 mg/day should be administered with caution.

Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the larger dose should be given before retiring.

***Geriatrics:*** In general elderly patients should be started on lowest possible doseof RIVOTRIL and observed closely(see WARNINGS AND PRECAUTIONS, Special Populations).

**Special Populations**

*Renal Impairment:* The safety and efficacy of clonazepam in patients with renal impairment has not been studied . Clonazepam metabolites are excreted by the kidneys; to avoid excessive accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. (see ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions).

*Hepatic Impairment:* Patients with severe hepatic impairment should not be treated with clonazepam (see CONTRAINDICATIONS). Patients with mild to moderate hepatic impairment should be given the lowest dose possible.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

***Symptoms:*** Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of RIVOTRIL (clonazepam) is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Increased frequency of seizures may occur in patients at supratherapeutic plasma concentrations (See ACTION AND CLINICAL PHARMACOLOGY, 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*
In managing overdosage, consider the possibility of multiple drug involvement.

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 cardio respiratory 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. Induction of vomiting is not generally recommended.

As in overdosage with other benzodiazepines, dialysis is of no known value in clonazepam overdosage.

If CNS depression is severe consider the use of flumazenil, a benzodiazepine receptor antagonist. The following should be kept in mind when flumazenil is used in the treatment of benzodiazepine overdosage:

- Flumazenil should only be administered under closely monitored conditions. In view of the short half life (about 1 hour) and duration of action of flumazenil, and the possible need for repeat doses, the patient should be closely monitored until all possible central benzodiazepine effects (e.g., resedation) have subsided.
- Particular caution is necessary when using flumazenil in cases of multiple drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside. Flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

***Warning:*** The benzodiazepine receptor antagonist 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.

Refer to the product monograph for flumazenil, for further information on the correct use of this drug.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

RIVOTRIL (clonazepam) has pharmacological properties characteristic of the benzodiazepine class of drugs. Clonazepam has sedative, hypnotic and anticonvulsant properties. As an anticonvulsant it is useful in the management of minor motor seizures (myoclonic seizures) and may be of some value in selected patients with absence spells (petit mal) who have failed to respond satisfactorily to the succinimides. Clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

### 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 around 90% with large differences between individuals.

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.

**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 metabolized by reduction to 7-amino-clonazepam and by N-acetylation to 7-acetamido-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.

**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 feces as metabolites. The urinary excretion of unchanged clonazepam is usually less than 2% of the administered dose.

**Special Populations and Conditions**

**Pediatric Patients:** 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.

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.

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

**Geriatrics**: The pharmacokinetics of clonazepam in the elderly has not been established.

**Hepatic Failure:** 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 disease 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.

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

## STORAGE AND STABILITY

Caution should be taken regarding storage. Keep in a tightly closed, light resistant container. Store at 15-30°C in the original package.

## SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of sight and reach of children.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

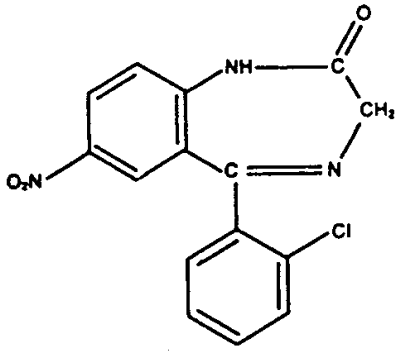
RIVOTRIL (clonazepam) is available as a 0.5 mg, pale orange, cylindrical, biplane, scored tablet, edges bevelled, with ROCHE 0.5 engraved on one face, scored on the other and as a 2.0 mg, white, cylindrical, biplane, scored tablet, edges bevelled, with ROCHE •2• on one side, cross-scored on the other. The 0.5 mg tablets are available in bottles of 100 and 500 tablets. The 2.0 mg tablets are available in bottles of 100 tablets.

The non-medicinal ingredients are as follows:
Tablets 0.5 mg: cornstarch, iron oxide red, iron oxide yellow, lactose, magnesium stearate, potato starch and talc.
Tablets 2 mg: cornstarch, lactose, magnesium stearate and microcrystalline cellulose.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

### Drug Substance

| | |
|---|---|
| Proper Name: | Clonazepam |
| Chemical Name: | 5-(2-chlorophenyl)-1, 3-dihydro-7-nitro-2H-1, 4-benzodiazepin-2-one. |
| Molecular Formula: | $C_{15}H_{10}ClN_3O_3$ |
| Molecular Mass: | 315.7 |
| Structural Formula: |  |
| Physiochemical properties: | Clonazepam is a white to yellow-white odourless fine powder. The pH of clonazepam is between 5.0 and 7.0 in 1% aqueous suspension. |
| Composition: | Each tablet contains either 0.5 mg or 2.0 mg clonazepam. |

## DETAILED PHARMACOLOGY

The pharmacological profile of clonazepam is the same as that of other anxiolytic sedative benzodiazepines. Its basic anticonvulsive properties are also similar to those of other diazepines.

**Relative Potency of Clonazepam and Other Anticonvulsants (Experimental Tests)**
The following table gives an indication of the relative potency of clonazepam and other anticonvulsants in various experimental tests in animals.

**Convulsant Test Oral $ED_{50}$ Values (mg/kg) in Mice and Humans**

| Drug | Max. Human Therapeutic Dose (mg/kg) | Metrazol Seizures | Thiosemi-carbazide Seizures | 30% Strychine Threshold | Maximum Electroshock |
|---|---|---|---|---|---|
| Clonazepam | 0.40 | 0.08 - 0.16 | 0.73 | 2.1 | 8.4 |
| Diazepam | 0.43 | 0.8 - 1.4 | 3.4 | 6.2 | 9.0 |
| Chlordiazepoxide | 1.43 | - | 27.0 | 22.2 | 17.2 |
| Phenobarbital | 8.5 | 8.0 - 27.0 | 63 | 37.2 | 7.3 |
| Trimethadione | 25.7 | 300 | 770 | - | 490 |
| DPH | 7.7 | - | 7800 | 7300 | 8.7 |

Clonazepam is effective in reducing photomyoclonic responses in baboons in doses under 0.5 mg/kg i.m. However, seizures evoked by local application of benzylpenicillin or strychnine do not respond well to systemic administration of clonazepam. Other CNS effects noted in several species at varying doses include taming, disinhibitory, sedative, ataxic, and hypnotic effects.

Blood pressure in dogs is lowered and vascular responses to serotonin and noradrenaline are inhibited by clonazepam in doses between 1 and 4 mg/kg i.v. There is a slight myocardial depressant action at these doses. Other pharmacologic effects occur only at higher doses in which gross CNS depressant effects are observed.

Metabolic pathways are similar in several species and the chief metabolites, 7-amino and 7-acetyl amino derivatives, have been isolated in urine of rats, dogs and humans. Hydroxylation also occurs as a prominent metabolic pathway. Metabolites are excreted primarily in urine, approximately 50% of an oral dose is excreted within seven days. Excretion of the drug plus metabolites increases as the dose increases.

## TOXICOLOGY

**Acute Toxicity**:
The following $LD_{50}$ values have been calculated for clonazepam:

| Species | Dose (mg/kg) and Route | | |
|---|---|---|---|
| | Oral | i.p. | i.v. |
| Mouse | >4000 | >800 | 2.85 $\pm$ 0.1 |
| Rat (adult) | >4000 | - | - |
| Rat (neonate) | 550 $\pm$ 120 | - | - |
| Rabbit | >2000 | - | - |

Signs of toxicity include decreased motor activity, ataxia, piloerection and tremors.

***Chronic Toxicity:*** Rats were fed clonazepam in the diet for 18 months in concentrations corresponding to 5, 20 and 50 mg/kg/day. No gross drug-related toxicity was evident. Slight and

transient elevations in liver function tests appeared in high dose animals corresponding to increases in liver weights, but these findings were not accompanied by histologic evidence of liver damage.

A study in dogs was conducted in which animals received clonazepam in doses of 3, 10 and 30 mg/kg/day for 12 months. Weight gain was reduced in mid- and high-dose animals compared to controls. The following significant changes in laboratory values were noted: a decrease in hemoglobin and hematocrit values in mid- and high-dose animals, a decreased albumin/globulin ratio due to decreased albumin and increased globulins in high-dose animals, increased alkaline phosphatase and bilirubin values in high-dose animals. There was a significant increase in liver weight in high-dose animals.

**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.

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

**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.

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

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

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## PART III: CONSUMER INFORMATION

**RIVOTRIL®**
clonazepam tablets

**This leaflet is part III of a three-part "Product Monograph" published when RIVOTRIL was approved for sale in Canada and is designed specifically for Consumers.**

**Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets, as you may need to read it again. If you are helping someone else to take RIVOTRIL, read this leaflet before you give the first tablet.**

**This leaflet is a summary and will not tell you everything about RIVOTRIL. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
RIVOTRIL is used for the treatment of certain types of seizures.

If you are 65 years or older, talk to your doctor before starting RIVOTRIL. RIVOTRIL may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

**What it does:**
RIVOTRIL contains the active ingredient clonazepam, which belongs to a group of medicines known as benzodiazepines. RIVOTRIL has anticonvulsant properties which help to manage seizures.

**When it should not be used:**
- If you are allergic to the group of medicines known as benzodiazepines (examples: diazepam, chlordiazepoxide, bromazepam, or flurazepam)
- If you are allergic to the medicinal ingredient (clonazepam)
- If you are allergic to any of the other non-medicinal ingredients it contains (see '**What the non-medicinal ingredients are**')
- If you suffer from lung disease.
- If you have a liver condition.
- If you have glaucoma.
- If you have myasthenia gravis.
- If you suffer from sleep apnea

**What the medicinal ingredient is:**
clonazepam.

**What the non-medicinal ingredients are:**
**Tablets 0.5 mg:** cornstarch, iron oxide red, iron oxide yellow, lactose, magnesium stearate, potato starch and talc.
**Tablets 2 mg:** cornstarch, lactose, magnesium stearate and microcrystalline cellulose.

**What dosage forms it comes in:**
RIVOTRIL is available as:
0.5 mg, pale orange, cylindrical, scored tablet, with ROCHE 0.5 engraved on one face, scored on the other.

2.0 mg, white, cylindrical, scored tablet, edges bevelled, with ROCHE •2• on one side, cross-scored on the other.

The 0.5 mg tablets are available in bottles of 100 and 500 tablets. The 2.0 mg tablets are available in bottles of 100 tablets.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Addiction, Abuse and Misuse: Even if you take RIVOTRIL exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take RIVOTRIL with:**
- **Opioids**
- **Alcohol or**
- **Ilicit drugs**

**Your doctor should:**
- **Talk to you about the risks of treatment with RIVOTRIL as well as other treatment (including non-drug) options**
- **Assess your risk for these behaviours before prescribing RIVOTRIL**
- **Monitor you while you are taking RIVOTRIL for the signs and symptoms of misuse and abuse. If you feel like you are craving RIVOTRIL, or not using it as directed, talk to your doctor right away.**

**Store RIVOTRIL in a secure place to avoid theft or misuse.**

**Withdrawal: If you suddenly stop taking RIVOTRIL, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see the Withdrawal section below)**
- **Always contact your doctor before stopping, or lowering your dose of RIVOTRIL or changing your medicine**

**RIVOTRIL with Opioids: Taking RIVOTRIL with opioid medicines can cause:**

- **Severe drowsiness**
- **Decreased awareness**
- **Breathing problems**
- **Coma**
- **Death**

**Withdrawal:**

- If you suddenly stop your treatment, lower your dose too fast, or witch to another medication, you can experience withdrawal symptoms that can range from mild to severe or life threatening. Some of your withdrawal symptoms can last for months after your stop RIVOTRIL.
- Your risk of going through withdrawal is higher if you are taking RIVOTRIL for a long time or at high doses. However, symptoms can still occur if you are taking RIVOTRIL as directed for a short period of time or slowly reducing the dose.
- The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).
- Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.
- Severe symptoms of withdrawal include:
  - Feeling like you cannot move or respond (catatonia)
  - Severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
  - Feeling depressed
  - Feeling disconnected from reality (dissociation)
  - Seeing or hearing things that are not there (hallucinations)
  - Overactive behaviour and thoughts (mania)
  - Believing in things that are not true (psychosis)
  - Convulsions (seizures), including some that do not stop
  - Thoughts or actions or suicide
- For other symptoms of withdrawal, see the **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM** table (below).
- To reduce your chances of going through withdrawal:
  - Always contact your doctor before stopping or reducing your dose of RIVOTRIL or changing medications
  - Always follow your doctor's instructions on how to reduce your dose carefully and safely
  - Tell your doctor **right away** if you experience any unusual symptoms after changing or stopping your treatment

**RIVOTRIL with Opioids:** Taking RIVOTRIL with opioid medicines can cause severe drowsiness and breathing problems.

- Tell your doctor if you:
  - Are taking opioid medicines
  - Are prescribed an opioid medicine after you start taking RIVOTRIL
- RIVOTRIL may affect your ability to be alert. Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and RIVOTRIL affects you. This effect of RIVOTRIL may be made worse if you take alcoholic drinks. If you increase your dose or change the timings of when you take your medication this may also modify your reactions.

**Falls and Fractures:** Benzodiazepines like RIVOTRIL can cause you to feel sleepy, dizzy and affect your balance**.** This increases the risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- Take other sedatives
- Consume alcohol
- Are elderly or
- Have a condition that causes weakness or frailty

- Benzodiazepines such as RIVOTRIL are not recommended for the primary treatment of psychotic illness
- Memory loss may occur when RIVOTRIL is used at therapeutic doses.
- Do not take this medicine if you are pregnant, or might become pregnant, unless advised by your doctor. Contact your doctor if you think you may be pregnant, or are intending to become pregnant. If you are pregnant or thinking about becoming pregnant, ask your healthcare provider about joining the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling (1-888) 233-2334 (toll free). Women who are pregnant and planning to take an antiepileptic drug should call the pregnancy registry to enable collection of valuable data about its use in pregnancy. Information on the registry can also be found at the website: http://www.aedpregnancyregistry.org/
- RIVOTRIL passes into breast milk. Therefore, if you

are breast feeding, this medicine should be avoided. Your doctor will discuss this with you.

- A small number of people being treated with anti-epileptics such as RIVOTRIL have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor immediately.

**BEFORE you use RIVOTRIL talk to your doctor or pharmacist if you:**

- Have a lung, liver or kidney condition.
- Have glaucoma.
- Are taking or plan on taking ANY other drugs (including herbal preparations, drugs you purchase without prescriptions, and those not prescribed by your doctor).
- Regularly drink alcohol or use recreational drugs.
- Suffer from a form of incoordination of the muscles called spinal or cerebellar ataxia.
- Have a history of depression and/or suicide attempts.
- Have rare hereditary problems of galactose intolerance.
- Have ever had a problem with:
  - Substance use, including prescribed or illegal drugs, or
  - Alcohol
- Have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

## INTERACTIONS WITH THIS MEDICATION

**Serious Drug Interactions**

**Taking RIVOTRIL and opioids may cause:**
- **Severe drowsiness**
- **Trouble breathing**
- **Coma**
- **Death**

**Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or health food store without a prescription.**

Some medicines may interfere with RIVOTRIL. These medicines include:

- medicines to control seizures
- narcotics and narcotic pain relievers (opioids, e.g., morphine, codeine; see **Serious Warnings and Precautions box**)
- muscle relaxants
- sleeping medication
- medicines to treat your mood, such as monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines
- phenytoin, phenobarbital, carbamazepine, and valproate.

These medicines may be affected by RIVOTRIL or may affect how well RIVOTRIL works. Your doctor or pharmacist can tell you what to do if you are taking any of these medicines.

**If you have not told your doctor about any of the above, tell him/her before you start taking RIVOTRIL.**

You must not consume alcohol while taking RIVOTRIL as its effects may worsen side effects that some patients experience with RIVOTRIL.

Grapefruit juice may increase blood levels of RIVOTRIL, therefore you should avoid drinking grapefruit juice while you are taking RIVOTRIL.

## PROPER USE OF THIS MEDICATION

**Usual dose:**
Always take the tablets exactly as your doctor tells you to. Your doctor will prescribe a suitable dose for you. The dose your doctor prescribes will depend on the nature of your illness, your reaction to the medicine, your age and body weight. The table below shows the different doses that your doctor may prescribe according to your age. Your doctor will start you on an initial low dose and gradually increase it until the desired effect is achieved.

| | Initial Dose | Maintenance Dose |
|---|---|---|
| Adults | 1.5 mg/day or less in divided doses | 8-10 mg/day in divided doses |
| Children (up to 10 years or 30kg) | 0.01-0.03 mg/kg/day in divided doses | 0.1-0.2 mg/kg/day in divided doses |

The total daily dose should be taken as advised by your doctor.

Do not change the prescribed dose yourself. If you think the effect of your medicine is too weak or too strong, talk to your doctor.

Your doctor will advise you when to stop taking the

medicine. Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Take the missed dose of RIVOTRIL as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take 2 doses at the same time.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications RIVOTRIL can cause some side effects. For most patients these side effects are likely to be minor and temporary as your body adjusts to the medicine. However, some may be serious. Consult your doctor or pharmacist as soon as you can if you do not feel well while taking RIVOTRIL.

The most common side effects are:
- Feeling drowsy or tired, especially at the start of treatment.
- Some muscle weakness and dizziness.
- Increased salivation.
- Movement control and balance issues.

Less common possible side effects are:
- Increased secretion from the lungs may occur. Children should therefore be watched carefully as this might cause difficulties in breathing and/or severe choking and coughing.
- In rare cases changes in your blood and liver may occur and your doctor will monitor for these.
- Falls and fractures

Withdrawal-related side effects:

- With long-term RIVOTRIL treatment development of physical and psychological dependence may occur. If treatment is stopped suddenly symptoms of withdrawal may occur, including: shaking, sweating, agitation/restlessness, sleep disturbances, anxiety (possibly extreme), headaches, muscle pain, tension, restlessness, confusion and irritability. In severe cases of withdrawal, symptoms may include numbness and tingling of the extremities, hallucinations (see or hear things that are not there), increased sensitivity to light, noise and physical contact.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Rare | Unusual behavioural problems (aggression, rage), sudden anxiety or excitation; restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behaviour. | | ✓ | |
| | Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes) | | | ✓ |
| | Depression Symptoms may include: difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, | | ✓ | |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| | helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced libido (sex drive). | | | |
| Uncommon | Suicidal Thoughts or Actions: Thoughts, plans and actions taken for the purpose of killing or harming yourself. | | ✓ | |
| **Unknown** | **Overdose**: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure. | | | ✓ |
| | **Respiratory Depression:** slow, shallow or weak breathing. | | | ✓ |

| SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM | | | | |
|---|---|---|---|---|
| **Symptom / effect** | | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | | **Only if severe** | **In all cases** | |
| | **Withdrawal: Severe symptoms include: Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide Other symptoms** | | ✓ | |

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| | **include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating. | | | |

***This is not a complete list of side effects. For any unexpected effects while taking RIVOTRIL, contact your doctor or pharmacist.***

## HOW TO STORE IT

- Keep RIVOTRIL in a cool dry place stored at room temperature (15-30°C) in the original package provided by the health care professional.
- Keep this medicine out of sight and reach of children.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

## MORE INFORMATION

**Reminder: This medicine has been prescribed only for you. Do not give it to anybody else. If you have any further questions, please ask your doctor or pharmacist.**

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-888-762-4388 (Drug Information).

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