PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PRO-CLONAZEPAM

Clonazepam Tablets

tablets, 0.5 mg, 1 mg and 2 mg, for oral use

USP

Anticonvulsant

PRO DOC LTÉE
2925 boul. Industriel
Laval, Quebec
H7L 3W9

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RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRO-CLONAZEPAM (clonazepam) is indicated for use:

- alone or as an adjunct in the management of myoclonic and akinetic seizures and petit mal variant (Lennox-Gastaut syndrome).
- 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 clonazepam. In some cases, dosage adjustment may re-establish efficacy.

PRO-CLONAZEPAM (clonazepam) is a benzodiazepine, available under the "Targeted" Schedule of the Controlled Drugs and Substances Act (CDSA IV) of Health Canada.

1.1 Pediatrics (<18 years of age)

See 4.2 Recommended Dose and Dosage Adjustment, Pediatrics; 7.1.3 Pediatrics; and 10.3 Pharmacokinetics, Special Populations, Pediatrics.

1.2 Geriatrics (>65 years of age)

Evidence from clinical studies and experience suggests that the use in the geriatric population is associated with differences in safety and effectiveness. See 7.1.4 Geriatrics; and 4.2 Recommended Dose and Dosage Adjustment, Geriatrics.

2 CONTRAINDICATIONS

- PRO-CLONAZEPAM is contraindicated in patients who are hypersensitive to other benzodiazepines, to this drug or to any other ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- PRO-CLONAZEPAM is contraindicated in patients with:
  - Severe respiratory insufficiency
  - Severe hepatic impairment as benzodiazepines may precipitate hepatic encephalopathy
  - Sleep apnea syndrome
  - Myasthenia gravis
  - Narrow angle glaucoma

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse, Misuse

The use of benzodiazepines, including PRO-CLONAZEPAM, 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 PRO-CLONAZEPAM.
- Monitor all patients regularly for the development of these behaviours or conditions.
- PRO-CLONAZEPAM should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like PRO-CLONAZEPAM, can produce severe or life-threatening withdrawal symptoms.

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

(see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant Use with Opioids

Concomitant use of PRO-CLONAZEPAM and opioids may result in profound sedation, respiratory depression, coma and death (see 7 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.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PRO-CLONAZEPAM (clonazepam) should always be prescribed at the lowest effective dose for the shortest duration possible.

Individualize dose: Dosage of PRO-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.
- **Drug-Drug Interactions**: See 9.4 Drug-Drug Interactions regarding pharmacokinetic and pharmacodynamic interactions with PRO-CLONAZEPAM.

- Avoid the concomitant use of opioids and PRO-CLONAZEPAM. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.
- The concomitant use of PRO-CLONAZEPAM with other anticonvulsants may increase depressant adverse effects. The dosage of each drug may need to be adjusted.

- **Geriatrics**: Elderly patients in particular may be more sensitive to benzodiazepines. See 7.1.4.Geriatrics.
  - Start with the lowest dose possible and observe closely.
  - Avoid long-term use of PRO-CLONAZEPAM.
  - Enhanced monitoring is recommended.
- **Hepatic / Renal Impairment**: PRO-CLONAZEPAM is contraindicated in patients with severe hepatic impairment. Patients with mild to moderate hepatic impairment should be given the lowest does possible. Proceed cautiously in cases of renal impairment. See Recommended Dose and Dosage Adjustment, Special Populations.

Potential loss of efficacy over time: 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 clonazepam. In some cases, dosage adjustment may re-establish efficacy.

Reduce dose/Discontinue gradually: PRO-CLONAZEPAM can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; 7 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.

4.2 Recommended Dose and Dosage Adjustment

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.

Pediatrics (<10 years of age or <30 kg of body weight):
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. See 10.3 Pharmacokinetics, Special Populations, Pediatrics.

Geriatrics (>65 years of age):
In general elderly patients should be started on lowest possible dose of PRO-CLONAZEPAM and observed closely. See 7.1.4 Geriatrics.

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 10.3 Pharmacokinetics, Special Populations and Conditions.

Hepatic Impairment: Patients with severe hepatic impairment should not be treated with clonazepam (see 2 CONTRAINDICATIONS). Patients with mild to moderate hepatic impairment should be given the lowest dose possible. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

4.3 Administration
For oral use. The tablets should be administered with water and swallowed without chewing.

4.4 Missed Dose
A missed dose should be taken as soon as possible, when noticed. But, if it is almost time for the next dose, the missed dose should be skipped, and the regular dosing schedule should be followed.

5 OVERDOSAGE

Symptoms: Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of PRO-CLONAZEPAM (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 10 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	Non-medicinal Ingrediens
Oral	Tablet 0.5 mg	Corn Starch, FD&C Yellow # 6 Lake, Lactose, Magnesium Stearate, and Microcrystalline Cellulose.
Oral	Tablet 1.0 mg	Corn Starch, FD&C Red # 40 Lake, Lactose, Magnesium Stearate, and Microcrystalline cellulose.
Oral	Tablet 2.0 mg	Corn Starch, Lactose, Magnesium Stearate, and Microcrystalline Cellulose.

PRO-CLONAZEPAM (clonazepam) is available as:

0.5 mg: Each round, orange, biplane tablet with beveled edges debossed “CLONAZEPAM” on one side and “0.5” under a score line on the other side. Available in bottles of 100, 500 and 1000 tablets.

1 mg: Each round pink, biconvex tablet debossed with “CLONAZEPAM” on one side and “1.0” on the other side. Available in HDPE bottles of 100, 500 and 1000 tablets.

2 mg: Each round, white, biplane tablet with bevelled edges, debossed with “CLONAZEPAM” on one side and “2.0” under a score line on the other side. Available in HDPE bottles of 100, 500 and 1000 tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

A paradoxical increase in seizure activity or the appearance of new seizure types has occurred in a very few patients during treatment with clonazepam. When used in patients in whom several different types of seizures coexist, PRO-CLONAZEPAM 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 PRO-CLONAZEPAM, 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 PRO-CLONAZEPAM. While PRO-CLONAZEPAM is being gradually withdrawn, the simultaneous substitution of incremental doses of another anticonvulsant may be indicated (also see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance, Withdrawal).

- **Concomitant use with opioids**

Concomitant use of benzodiazepines, including PRO-CLONAZEPAM, 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.

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 PRO-CLONAZEPAM 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 PRO-CLONAZEPAM than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking PRO-CLONAZEPAM, 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 5 OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when PRO-CLONAZEPAM is used with opioids.

Advise patients not to drive or operate heavy machinery during the concomitant use of PRO-CLONAZEPAM and an opioid.

- **Concomitant use of alcohol/CNS depressants**

The concomitant use of PRO-CLONAZEPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of clonazepam possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see 9.4 Drug-Drug Interactions, Pharmacodynamic DDIs; and 5 OVERDOSAGE).

PRO-CLONAZEPAM should be used only with particular caution 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.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity.

Dependence/Tolerance

Use of benzodiazepines, such as PRO-CLONAZEPAM, 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 me dicines, 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 PRO-CLONAZEPAM 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, history of alcohol or drug abuse and concomitant drug use, prior to prescribing PRO-CLONAZEPAM. In individuals prone to substance use disorder, PRO-CLONAZEPAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- PRO-CLONAZEPAM 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 PRO-CLONAZEPAM, 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 be 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.

Driving and Operating Machinery
Patients receiving PRO-CLONAZEPAM 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 benzodiazepines 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 9 DRUG INTERACTIONS). They also should be warned against the concomitant use of alcohol and other CNS depressant drugs.

Endocrine and Metabolism

- **Porphyria**

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

- **Lactose intolerance**

Lactose is a non-medicinal ingredient in PRO-CLONAZEPAM. Therefore, patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Gastrointestinal

- **Hypersalivation**

PRO-CLONAZEPAM 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, PRO-CLONAZEPAM should be used with caution in patients with chronic respiratory diseases.

Hepatic/Biliary/Pancreatic
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in severe hepatic impairment. Special caution should be exercised when administering PRO-CLONAZEPAM to patients with mild to moderate hepatic impairment (see 2 CONTRAINDICATIONS; 4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment).

Monitoring and Laboratory Tests
Periodic liver function tests and blood counts are recommended during long-term therapy with PRO-CLONAZEPAM.

Neurologic

- **CNS, Psychosis and Depression**

PRO-CLONAZEPAM should be used with particular caution in patients with ataxia.

Benzodiazepines are not recommended for the primary treatment of psychotic illness. See 7 WARNINGS AND PRECAUTIONS, Psychiatric, Psychiatric and 'paradoxical' reactions.
Patients with a history of depression and/or suicide attempts should be kept under close supervision. See 7 WARNINGS AND PRECAUTIONS, Psychiatric, Suicidal Ideation and Behaviour.

- **Amnesia**

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

- **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.

Psychiatric

- **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.

- **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.

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 4.2 Recommended Dose and Dosage Adjustment, Hepatic Impairment; 10.3 Pharmacokinetics, - Metabolism; and -Special Populations, Renal Insufficiency.

Reproductive Health: Female and Male Potential
See 7.1.1

Respiratory
Respiratory depression may occur following administration of PRO-CLONAZEPAM. 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 PRO-CLONAZEPAM should be instituted with caution in patients with chronic respiratory diseases (see 2 CONTRAINDICATIONS).

Hypersecretion in the upper respiratory passages has at times been a troublesome adverse reaction during clonazepam 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.

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY).

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 clonazepam, physicians are advised to recommend that pregnant patients taking clonazepam 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/.**

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

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 PRO-CLONAZEPAM is important in pediatric patients. See 4.2 Recommended Dose and Dosage Adjustment, Pediatrics; 10.3 Pharmacokinetics, Special Populations, Pediatrics.

7.1.4 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 PRO-CLONAZEPAM 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 PRO-CLONAZEPAM 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Most Frequent Adverse Reactions:

The most frequently occurring adverse reactions of 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 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

8.2 Clinical Trial Adverse Reactions
This information is not available for this product.

8.3 Less Common Clinical Trial Adverse Reactions
This information is not available for this product.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

This information is not available for this product.

8.5 Post-Market Adverse Reactions

Other adverse reactions listed by system organ class in alphabetical order, are:

System Organ Class	Adverse Reaction(s)
Blood and Lymphatic System Disorders	Anaemia, leukopenia (WBC below 4000/cu mm), decreased platelet count (thrombocytopenia), eosinophilia and lymphadenopathy.
Cardiac Disorders	Palpitations, cardiac failure including cardiac arrest.
Endocrine Disorders	Gynecomastia, isolated cases of reversible development of premature secondary sexual characteristics in children (incomplete precocious puberty).

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

System Organ Class	Adverse Reaction(s)
Gastrointestinal Disorders	Increased salivation, nausea, vomiting, anorexia, constipation, diarrhoea, encopresis, dry mouth, increased appetite, abdominal pain, sore gums, gastritis, epigastric symptoms and coated tongue.
General Disorders and Administration Site Conditions	Fever, general deterioration.
Hepatobiliary Disorders	Hepatomegaly.
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.
Investigations	Transient elevations of serum transaminase and alkaline phosphatase.
Metabolism and Nutrition Disorders	Weight gain or loss, dehydration.
Musculoskeletal and Connective Tissue Disorders	Pains such as low back pain.
Nervous System Disorders	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.

System Organ Class	Adverse Reaction(s)
Psychiatric Disorders	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. Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as PRO-CLONAZEPAM. Severe and life-threatening symptoms have been reported. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)
Renal and Urinary Disorders	Rare instances of dysuria, nocturia, urinary incontinence, urinary retention and enuresis.
Respiratory, Thoracic and Mediastinal Disorders	Chest congestion, hypersecretion in the upper respiratory passages, rhinorrhea, shortness of breath, dyspnea and respiratory depression.
Skin and Subcutaneous Tissue Disorders	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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of PRO-CLONAZEPAM 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 7 WARNINGS AND PRECAUTIONS, General, Risks from Concomitant use with Opioids.)

9.2 Drug Interactions Overview

Simultaneous administration of several anticonvulsant drugs may be considered with PRO-CLONAZEPAM (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 clonazepam. When used in patients in whom several different types of seizures coexist, clonazepam 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.

9.3 Drug-Behavioural Interactions

The concomitant use of PRO-CLONAZEPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of clonazepam possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression. See Drug-Drug Interactions, Pharmacodynamic DDIs.

9.4 Drug-Drug Interactions

The drugs listed hereinafter are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of interaction (i.e., those identified as contraindicated).

- **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 up to 38% during combined treatment.

Clonazepam 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 clonazepam 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 clonazepam have not been clearly identified but include CYP3A4. Inhibitors of CYP3A4 (e.g., fluconazole) may impair the metabolism of clonazepam 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 PRO-CLONAZEPAM 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 PRO-CLONAZEPAM 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 7 WARNINGS AND PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines, Concomitant use of Alcohol/CNS Depressants; 5 OVERDOSAGE).

Opioids

Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including PRO-CLONAZEPAM, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patie nts 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 7 WARNINGS AND PRECAUTIONS, Risks from concomitant use of opioids and benzodiazepines). Patients should be advised not to drive if they are taking both PRO-CLONAZEPAM and opioids.

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.

9.5 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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

PRO-CLONAZEPAM (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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

Absorption

Clonazepam is rapidly and almost completely absorbed after oral administration of clonazepam 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

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

11 STORAGE, STABILITY AND DISPOSAL

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

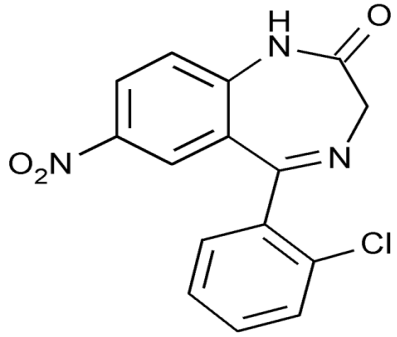
12 SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 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:	315.71 g/mol
Structural formula:	
Physicochemical properties:	Light yellow powder, having a faint odor. Melts at about 239°C. Insoluble in water; sparingly soluble in acetone and in chloroform; slightly soluble in alcohol and in ether.

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.

Table: 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.

14 CLINICAL TRIALS

The clinical trial data on which the original indications were authorized is not available.

14.2 Comparative bioavailability studies

A blinded, randomized, two-treatment, two-sequence, two-period, single oral dose (1 x 2 mg), crossover comparative bioavailability study of PRO-CLONAZEPAM tablets 2 mg (Pro Doc Ltée) and RIVOTRIL® tablets 2 mg (Hoffman-La Roche Ltd.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 18 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clonazepam (1 x 2 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	392.02 398.22 (17.48)	364.95 372.26 (19.86)	107.4	99.8 – 115.6
AUC (ng.h/mL)	459.71 466.40 (16.84)	428.70 434.63 (16.70)	107.2	100.5-114.5
C_{MAX} (ng/mL)	10.56 10.71 (15.90)	10.03 10.21 (19.19)	105.3	95.6-116.1
T_{MAX}[3] (h)	2.57 (1.81)	2.56 (2.31)		
$T_{1/2}$[3] (h)	35.93 (7.32)	34.06 (7.06)		

[1]PRO-CLONAZEPAM (clonazepam) tablets, 2 mg (Pro Doc Ltée)

[2]Rivotril® (clonazepam) tablets, 2 mg (Hoffman-La Roche Ltd, Canada)

[3]Expressed as the arithmetic mean (CV%) only.

A blinded, randomized, two-treatment, two-sequence, two-period, single oral dose (4 x 0.5 mg), crossover comparative bioavailability study of PRO-CLONAZEPAM tablets 0.5 mg (Pro Doc Ltée) and RIVOTRIL® tablets 0.5 mg (Hoffman-La Roche Ltd.), was conducted in healthy, adult male subjects under fasting conditions. Comparative bioavailability data from 26 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clonazepam (4 x 0.5 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90%Confidence Interval
$AUC_{0\text{-}72h}$ (ng.h/mL)	272.35 276.82 (17.1)	261.83 265.88 (18.0)	104.0	(98.5 - 109.8)
AUC_T (ng.h/mL)	328.96 337.02 (20.2)	302.50 308.80 (20.4)	108.8	(101.7 - 116.3)
AUC_∞ (ng.h/mL)	410.96 421.20 (21.0)	375.80 382.72 (19.1)	109.4	101.2 - 118.1)
C_{MAX} (units)	8.64 8.74 (16.6)	7.85 7.97 (18.4)	110.1	(104.5 - 115.9)
T_{MAX}[3] (h)	1.94 (0.73)	2.60 (1.42)		
$T_{½}$[3] (h)	47.77 (11.7)	42.39 (16.8)		

[1]PRO-CLONAZEPAM (clonazepam) tablets, 0.5 mg (Pro Doc Ltée)
[2]Rivotril® (clonazepam) tablets, 0.5 mg (Hoffman-La Roche Ltd, Canada)
[3]Expressed as the arithmetic mean (CV%) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

- **Acute Toxicity Studies**

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 ± 0.1
Rat (adult)	>4000	-	-
Rat (neonate)	550 ± 120	-	-
Rabbit	>2000	-	-

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

- **Chronic Toxicity Studies**

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.

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

Reproductive and Developmental Toxicology:

- **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.

17 SUPPORTING PRODUCT MONOGRAPH

RIVOTRIL® tablets, 0.5 mg and 2 mg, submission control 256297, Product Monograph, CHEPLAPHARM Arneimittel GmbH. APR 28, 2022

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PRO-CLONAZEPAM

clonazepam tablets

Read this carefully before you start taking **PRO-CLONAZEPAM** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PRO-CLONAZEPAM**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take PRO-CLONAZEPAM 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 PRO-CLONAZEPAM with:

- **Opioids**
- **Alcohol or**
- **Illicit drugs**

Your healthcare professional should:

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

Store PRO-CLONAZEPAM in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking PRO-CLONAZEPAM, 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 PRO-CLONAZEPAM or changing your medicine.**

PRO-CLONAZEPAM with Opioids: Taking PRO-CLONAZEPAM with opioid medicines can cause:

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

What is PRO-CLONAZEPAM used for?

PRO-CLONAZEPAM is used alone or with other anti-seizure medicines to treat certain types of seizures called:

- myoclonic seizures,

- akinetic seizures,
- petit mal seizures in patients who suffer from Lennox-Gastaut syndrome, a type of epilepsy and
- petit mal seizures in patients who do not respond to anti-seizure medicines called succinimides.

If you are 65 years or older, talk to your healthcare professional before starting PRO-CLONAZEPAM. PRO-CLONAZEPAM may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does PRO-CLONAZEPAM work?
PRO-CLONAZEPAM contains the active ingredient clonazepam. Clonazepam belongs to a group of medicines called benzodiazepines. It can slow down electrical impulses in the brain that cause seizures.

What are the ingredients in PRO-CLONAZEPAM?
Medical ingredient: clonazepam

Non-medicinal ingredients: Corn Starch, FD&C Yellow # 6 Lake (0.5 mg), FD&C Red # 40 Lake (1 mg) Lactose, Magnesium Stearate, and Microcrystalline Cellulose.

PRO-CLONAZEPAM comes in the following dosage forms:
PRO-CLONAZEPAM Tablet: 0.5 mg, 1 mg and 2 mg.

Do not use PRO-CLONAZEPAM if you/your child:
- are allergic to the group of medicines known as benzodiazepines (such as diazepam, chlordiazepoxide, bromazepam, or flurazepam).
- are allergic to clonazepam. or to any other ingredient in PRO-CLONAZEPAM.
- have severe breathing problems.
- have severe liver problems.
- have narrow angle glaucoma (increased pressure in the eye).
- have myasthenia gravis (muscle weakness).
- suffer from sleep apnea (pauses in breathing during sleep).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you/your child take PRO-CLONAZEPAM. Talk about any health conditions or problems you may have, including if you/your child:
- have lung or breathing problems.
- have liver or kidney problems.
- regularly or occasionally drink alcohol or use recreational drugs. Do not drink alcohol while taking PRO-CLONAZEPAM without first talking to your healthcare professional.
- suffer from ataxia (inability to coordinate muscle movements).
- have a history of depression and/or suicide attempts.
- are lactose intolerant or have one of the following rare hereditary diseases:
    - galactose intolerance,
    - total lactase deficiency,
    - glucose-galactose malabsorption.

- 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).
- have porphyria (a condition that affects the nervous system and skin).
- are 65 years of age or older.

Other warnings you should know about:

Do not stop your treatment with PRO-CLONAZEPAM without first checking with your healthcare professional. This could lead to a sudden worsening of your seizures.

Worsening Seizures: During treatment with PRO-CLONAZEPAM, your seizures may get worse or you may develop a new type of seizure. If you start to have more seizures or your seizures get worse, tell you healthcare professional right away.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch 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 PRO-CLONAZEPAM.

Your risk of going through withdrawal is higher if you are taking PRO-CLONAZEPAM for a long time or at high doses. However, symptoms can still occur if you are taking PRO-CLONAZEPAM 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 of suicide.

For other symptoms of withdrawal, see the **Serious side effects 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 PRO-CLONAZEPAM 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.

Driving and Using Machines: PRO-CLONAZEPAM may affect your ability to be alert. It may make you feel dizzy, drowsy and affect your coordination. These effects may be worse if you drink alcohol, increase your dose or change the timings of when you take your medication.

While you are taking PRO-CLONAZEPAM, **do not** drive, use machinery, or do activities that require you to be alert:

- for the first few days, or until you know how PRO-CLONAZEPAM affects you.
- if you are also taking an opioid medicine.

Falls and Fractures: Benzodiazepines like PRO-CLONAZEPAM 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.

Mental and Behavioural Changes: A variety of abnormal thinking and behaviour changes may occur when you take PRO-CLONAZEPAM. Some of these changes include aggressiveness, irritability, agitation, anger, delusions, strange behaviour, anxiety, nightmares, restlessness, hallucinations, and inappropriate behaviour. If you develop any unusual thoughts or behaviour while using PRO-CLONAZEPAM, tell your healthcare professional right away

Self-harm or Suicide: If you have thoughts of harming or killing yourself at any time, contact your healthcare professional or go to a hospital **right away**. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you if they:

- think your depression or mental illness is getting worse, or
- are worried about changes in your behaviour

Pregnancy and breastfeeding:

- If you take PRO-CLONAZEPAM during pregnancy, your baby is at risk for serious birth defects, and cognitive disabilities.
- Tell your healthcare professional right away if you become pregnant or think you are pregnant during treatment with PRO-CLONAZEPAM. You and your healthcare professional should decide if you will continue to take PRO-CLONAZEPAM while you are pregnant.
- **Pregnancy Registry:** If you become pregnant while taking clonazepam, talk to your healthcare professional about registering with the North American Antiepileptic Drug Pregnancy Registry.

You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy. Information about the registry can also be found at the website: http://www.aedpregnancyregistry.org/.

- PRO-CLONAZEPAM passes into breast milk and may harm your baby. Do not breastfeed during treatment with PRO-CLONAZEPAM. Talk to your healthcare professional about the best way to feed your baby during this time.

Check-ups and testing: PRO-CLONAZEPAM may cause changes in your blood and liver. During long-term treatment with PRO-CLONAZEPAM, your healthcare professional may perform tests to monitor your blood count and liver.

Amnesia: PRO-CLONAZEPAM can cause a type of memory loss known as amnesia. This is more likely to happen with higher doses of PRO-CLONAZEPAM.

Hypersecretion: PRO-CLONAZEPAM can cause increased secretion from the lungs (hypersecretion). Children should be watched carefully as this might cause difficulties in breathing and/or severe choking and coughing.

Tell your healthcare professional about all the medicines you/your child take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PRO-CLONAZEPAM:

Serious Drug Interactions

Taking PRO-CLONAZEPAM and opioids may cause:

- **severe drowsiness**
- **trouble breathing**
- **coma**
- **death**

Tell your healthcare professional if you:

- **are taking opioid medicines**
- **are prescribed an opioid medicine after you start taking PRO-CLONAZEPAM**

- other medicines to control seizures such as phenytoin, phenobarbital, carbamazepine, lamotrigine and valproate
- muscle relaxants
- medicines used to treat depression such as Monoamine Oxidase Inhibitors (MAOIs) and tricyclic antidepressants
- hypnotics and sedatives such as barbiturates, used to treat anxiety or sleep problems
- antihistamines, used to treat allergies
- antipsychotics, used to treat mental health problems
- fluconazole, used to treat fungal infections
- alcohol. **Do not** consume alcohol when taking PRO-CLONAZEPAM.
- grapefruit juice. Avoid drinking grapefruit juice or eating grapefruit when taking PRO-CLONAZEPAM.

How to take PRO-CLONAZEPAM:

- Take PRO-CLONAZEPAM exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Swallow the tablets with water. DO NOT chew the tablets.

Usual dose:
Adults and Children:
Your healthcare professional will determine the dose that is right for you/your child. Your/your child's dose and how often you/your child take it will depend on your/your child's age, weight, other medical conditions, and severity of your/your child's seizures.

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

Overdose:
Signs of an overdose with PRO-CLONAZEPAM include:

- drowsiness,
- involuntary eye movements (side-to-side, up and down, circular motion),
- lack of muscle control or coordination,
- below normal or absence reflexes,
- low blood pressure,
- breathing or lung problems,
- coma.

If you think you, or a person you are caring for, have taken too much PRO-CLONAZEPAM, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you/your child missed a dose of this medication, take it as soon as you/your child remember. However, if it is almost time for your/your child's next dose, skip the missed dose and continue with your/your child's next scheduled dose. Go back to the regular dosing schedule. Do not take two doses at the same time.

What are possible side effects from using PRO-CLONAZEPAM?
These are not all the possible side effects you may have when taking PRO-CLONAZEPAM. If you experience any side effects not listed here, tell your healthcare professional.

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 (hypersecretion).
- Falls and fractures.

Other side effects may include:

- Fever, nausea, vomiting, constipation, diarrhea and headache
- Dry mouth
- Increased or decreased appetite
- Pain in the abdomen or lower back
- Sore gums
- Increased or decreased libido
- Weight gain or loss
- Dehydration
- Seeing double
- Trouble falling asleep
- Tremors
- Slurred speech

Serious side effects 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**	
UNCOMMON			
Self-harm or Suicide: thoughts or actions about hurting or killing yourself		✓	
RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and activities with friends, reduced libido (sex drive) and thoughts of death or suicide. If you have a history of depression, your depression may become worse		✓	
Mental and Behavioural Changes: unusual 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		✓	
UNKNOWN FREQUENCY			
Amnesia (a type of memory loss): difficulty recalling events that recently happened		✓	
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.			✓

Serious side effects 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**	
Respiratory Depression: slow, shallow or weak breathing.			✓
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): uncontrollable shaking, with or without loss of consciousness. **Thoughts or actions of suicide.** **Other symptoms 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.		✓	
Worsening seizures		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

Store PRO-CLONAZEPAM at room temperature (15-30°C) in the original light-resistant package provided by the healthcare professional.

Keep out of reach and sight of children.

If you want more information about PRO-CLONAZEPAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or by contacting Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or medinfo@prodoc.qc.ca.

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