

PRODUCT MONOGRAPH

 **TEVA-CLONAZEPAM**

Clonazepam Tablets

0.5 mg and 2 mg

USP

Anticonvulsant

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada M1B 2K9
www.tevacanada.com

Date of Revision: December 7, 2021

Control#: 253634

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	12
DRUG INTERACTIONS	14
DOSAGE AND ADMINISTRATION.....	16
OVERDOSAGE.....	17
ACTION AND CLINICAL PHARMACOLOGY	18
STORAGE AND STABILITY	20
SPECIAL HANDLING INSTRUCTIONS	20
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	20
PART II: PHARMACEUTICAL INFORMATION	22
PHARMACEUTICAL INFORMATION	22
CLINICAL TRIALS.....	23
DETAILED PHARMACOLOGY	24
TOXICOLOGY.....	25
REFERENCES.....	27
PART III: CONSUMER INFORMATION.....	29

TEVA-CLONAZEPAM
Clonazepam Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet / 0.5 mg	Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, Magnesium Stearate, and FD&C Yellow #6
Oral	Tablet / 2 mg	Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, and Magnesium Stearate

INDICATIONS AND CLINICAL USE

TEVA-CLONAZEPAM (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).

TEVA-CLONAZEPAM 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 clonazepam. 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 TEVA-CLONAZEPAM and observed closely. Long-term use of TEVA-CLONAZEPAM 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 TEVA-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 TEVA-CLONAZEPAM
- Monitor all patients regularly for the development of these behaviours or conditions.
- TEVA-CLONAZEPAM should be stored securely to avoid theft or misuse.

Withdrawal

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

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

(see WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant use with Opioids

Concomitant use of TEVA–CLONAZEPAM 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 very few patients during treatment with clonazepam. When used in patients in whom several different types of seizures coexist, TEVA–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 TEVA–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 TEVA–CLONAZEPAM. While TEVA–CLONAZEPAM 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 TEVA–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 (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 TEVA–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 TEVA–CLONAZEPAM than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking TEVA–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 OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM to patients with mild to moderate hepatic impairment (see CONTRAINDICATIONS).

CNS, psychosis and depression

TEVA-CLONAZEPAM 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 clonazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of TEVA-CLONAZEPAM possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see DRUG INTERACTIONS and OVERDOSAGE).

TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM. 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

TEVA-CLONAZEPAM 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 TEVA-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 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 TEVA-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 and concomitant drug use, prior to prescribing TEVA-CLONAZEPAM. In individuals prone to substance use disorder, TEVA-CLONAZEPAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- TEVA-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 TEVA-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 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 TEVA-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 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 TEVA-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 TEVA-CLONAZEPAM 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 clonazepam therapy, especially in small mentally retarded children who ordinarily have difficulty 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

TEVA-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, TEVA-CLONAZEPAM 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 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/>.

Nursing Women: Although the active ingredient of TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM is important in pediatric 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 TEVA-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 TEVA-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.

Monitoring and Laboratory Tests

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

ADVERSE REACTIONS

Adverse Drug 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 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 TEVA-CLONAZEPAM. 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, dysdiadokinesia, 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 TEVA-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 WARNINGS AND PRECAUTIONS, General, Risks from Concomitant use with Opioids)

Overview

Simultaneous administration of several anticonvulsant drugs may be considered with TEVA-CLONAZEPAM (clonazepam), however, it should be borne in mind that the use of multiple anticonvulsants 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, TEVA-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.

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.

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 TEVA-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 TEVA-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 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 clonazepam, 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 TEVA-CLONAZEPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM (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 TEVA-CLONAZEPAM is added to an already existing anticonvulsant regimen.
- TEVA-CLONAZEPAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM 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 0.5 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 dose of TEVA-CLONAZEPAM 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 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 overdose, 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 overdose with other benzodiazepines, dialysis is of no known value in clonazepam overdose.

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 overdose:

- 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., re sedation) have subsided.
- Particular caution is necessary when using flumazenil in cases of multiple drug overdose, 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

TEVA-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.

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

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

Clonazepam tablets should be stored in tightly closed, light-resistant containers at 15–30°C.

SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA–CLONAZEPAM (clonazepam) is available as:

0.5mg: orange-coloured, round, flat faced, bevelled edged, single scored compressed tablets, debossed modified N over N with an engraving cut in between on one side and 0.5 on the reverse.

2.0mg: white, round, flat faced bevelled-edged, single scored compressed tablets, debossed modified N over N with an engraving cut in between on one side and 2 on the reverse.

Supplied in bottles of 100 and 500.

The non-medicinal ingredients are as follows:

Tablets 0.5 mg: Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, Magnesium Stearate, FD&C Yellow #6.

Tablets 2 mg: Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, Magnesium Stearate.

PART II: SCIENTIFIC INFORMATION

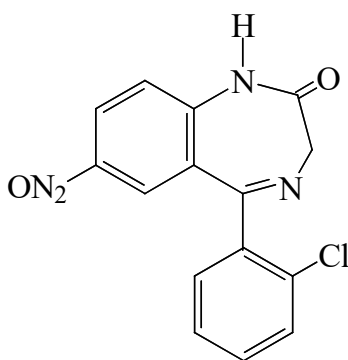
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Clonazepam Tablets

Chemical Name: 5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one

Structural Formula:



Molecular Formula: C₁₅H₁₀ClN₃O₃

Molecular Weight: 315.72 g/mol

Description: Clonazepam is a light yellow powder, having a faint odor. It melts at about 239°C. It is insoluble in water, sparingly soluble in acetone and in chloroform, slightly soluble in alcohol and in ether.

CLINICAL TRIALS

Comparative Bioavailability Studies

A two way, single-dose (4 x 0.5 mg), crossover comparative bioavailability study of Teva-Clonazepam (Teva Canada Limited) and Rivotril® (Hoffmann-La Roche Limited, Canada), was conducted in healthy adult subjects under fasting conditions. The results obtained from the 12 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 _T (ng·h/mL)	394.1 399.9 (15.7)	388.9 394.3 (16.9)	101.3	97.6 – 105.2
AUC ₀₋₇₂ (ng·h/mL)	320.8 325.3 (17.1)	318.5 323.5 (18.2)	100.7	97.7 – 103.9
AUC _I (ng·h/mL)	436.5 441.2 (14.7)	434.9 439.4 (14.5)	100.4	97.2 – 103.7
C _{max} (ng/mL)	9.3 9.4 (17.8)	9.8 9.9 (19.9)	95.0	89.4 – 100.9
T _{max} ³ (h)	2.9 (1.5)	2.0 (0.8)		
T _{1/2} ³ (h)	37.3 (7.4)	37.8 (6.6)		

¹ Teva-Clonazepam 0.5 mg tablets manufactured by Teva Pharmaceutical Industries Ltd.

² Rivotril® 0.5 mg tablets by Hoffmann-La Roche Limited, Canada were purchased in Canada

³ Expressed as the arithmetic mean (CV%) only

A two way, single dose (1 x 2 mg) crossover comparative bioavailability study of Teva-Clonazepam (Teva Canada Limited) and Rivotril® (Hoffmann-La Roche Limited, Canada) was

conducted in healthy adult subjects under fasting conditions. The results obtained from the 16 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Clonazepam (1 x 2mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test ¹	Reference ²	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng·h/mL)	391.0 396.8 (18.9)	389.1 394.3 (16.8)	100.5	96.8 - 104.3
AUC ₀₋₇₂ (ng·h/mL)	299.7 304.0 (18.7)	299.8 303.5 (16.2)	100.0	96.0 - 104.1
AUC _I (ng·h/mL)	423.8 431.3 (20.6)	422.8 429.0 (17.5)	101.7	98.3 – 105.4
C _{max} (ng/mL)	8.9 9.1 (20.3)	8.8 8.9 (17.9)	101.1	95.8 - 106.8
T _{max} ³ (h)	3.5 (34.2)	3.1 (51.7)		
T _{1/2} ³ (h)	38.7 (17.7)	38.7 (20.8)		

¹ Teva-Clonazepam 2 mg tablets manufactured by Teva Pharmaceutical Industries Ltd.

² Rivotril® 2 mg tablets by Hoffmann-La Roche Limited, Canada were purchased in Canada

³ Expressed as the arithmetic mean (CV%) only

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 diazepam.

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 ED₅₀ Values (mg/kg) in Mice and Humans

Drug	Max. Human Therapeutic Dose (mg/kg)	Metrazol Seizures	Thiosemi-carbazide Seizures	30% Strychnine Threshold	Maximum Electro-shock
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 LD₅₀ 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: 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 sternbrae and limb defects) was observed.

REFERENCES

1. Blum JE, Haefely W, Jalfre M, et al. Pharmakologie und toxikologie des antiepileptikums clonazepam. *Arzneimittel-Forschung* 1973; 23: 377–89.
2. Guerrero-Figueroa R, et al. Effects of two benzodiazepine derivatives on cortical and subcortical epileptogenic tissues in the cat and monkey. *Curr Therap Res* 1969;11:27-50.
3. Schallek W, et al. Recent developments in the pharmacology of the benzodiazepines, advances in pharmacology and chemotherapy. Academic Press, Inc., New York and London 1972;10:132-7.
4. Stark LG, et al. The anticonvulsant effects of phenobarbital, diphenylhydantoin and two benzodiazepines in the baboon, *Papio Papio*. *J Pharmacol Exp Therap* 1970;173:125-32.
5. Barnett AM. Treatment of epilepsy with clonazepam (Ro 5-4023). *S.A. Medical Journal* 1973;47:1683-6.
6. Browne TR. Clonazepam: A review of a new anticonvulsant drug. *Arch Neurol* 1976; 33: 326–32.
7. Carson MJ et al. Treatment of minor motor seizures with clonazepam. *Develop Med Child Neurol* 1975; 17: 306–10.
8. Dreifus FE, et al. Serum clonazepam concentrations in children with absence seizures. *Neurology* 1975;25:255-8.
9. Fazio C, et al. Treatment of epileptic seizures with clonazepam. *Arch Neurol* 1975; 32: 304–7.
10. Gastaut H. Propriétés anti-épileptiques exceptionnelles d'une benzodiazépine nouvelle le Ro 5-4023. *Vie Med* 1970;51:5175-88.
11. Hanson RA, et al. A new anticonvulsant in the management of minor motor seizures. *Develop Med Child Neurol* 1972; 14: 3–14.
12. Hollister LE et al. Dose-ranging studies of clonazepam in man. *Psychopharmacology Communications* 1975; 1: 89–92.
13. Hooshmand H. Intractable seizures; treatment with a new benzodiazepine anticonvulsant. *Arch Neurol* 1972;27:205-8.
14. Mekkelsen B, et al. A clinical study of benzodiazepine Ro 5-4023 (clonazepam) in the treatment of epilepsy. *Acta Neurol Scand* 1973;49:91-6.

15. Negrin P, et al. Antiepileptic properties of Ro 5-4023 by mouth. Report of 40 cases. *Electroenceph Clin Neurophysiol* 1971;31:528-34.
16. Rose SW, et al. Serum clonazepam concentrations in children with absence seizures. *Neurology* 1974;24:386-90.
17. Sjö O, et al. Pharmacokinetics and side-effects of clonazepam and its 7-amino-metabolite in man. *Eur J Clin Pharmacol* 1975; 8: 249-54.
18. Turner M, et al. Clinical EEG evaluation of a new benzodiazepine derivative (Ro 5-4023) by oral administration in epileptic patients using the double-blind technique. *Electroenceph Clin Neurophysiol* 1971;31:628-30.
19. Product Monograph for Rivotril® (clonazepam) by Hoffmann-LaRoche Ltd. Vaudreuil, Quebec, June 02, 2021. Control Number: 245341
20. A Two-Way, Single-Dose Bioavailability Study of Clonazepam 0.5 mg Tablets in Normal, Healthy Male Volunteers. Completed November, 1992.
21. A Two-Way Single-Dose Fasting Bioavailability Study of Clonazepam 2 mg Tablets in Normal, Healthy, Non-Smoking Male Volunteers. Completed August, 1996.

PART III: CONSUMER INFORMATION

**TC TEVA-CLONAZEPAM
clonazepam tablets**

This leaflet is part III of a three-part "Product Monograph" published when TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM, read this leaflet before you give the first tablet.

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

ABOUT THIS MEDICATION

What the medication is used for:

TEVA-CLONAZEPAM is used for the treatment of certain types of seizures.

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

What it does:

TEVA-CLONAZEPAM contains the active ingredient clonazepam, which belongs to a group of medicines known as benzodiazepines. TEVA-CLONAZEPAM 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: Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, Magnesium Stearate, and FD&C Yellow #6.

Tablets 2 mg: Lactose Monohydrate, Croscarmellose Sodium, Microcrystalline Cellulose, Polysorbate, Glycerin, Colloidal Silicon Dioxide, and Magnesium Stearate.

What dosage forms it comes in:

TEVA-CLONAZEPAM is available as:

0.5 mg: orange-coloured, round, flat faced, bevelled edged, single scored compressed tablets, debossed modified N over N with an engraving cut in between on one side and 0.5 on the reverse.

2.0 mg: white, round, flat faced bevelled-edged, single scored compressed tablets, debossed modified N over N with an engraving cut in between on one side and 2 on the reverse.

Supplied in bottles of 100 and 500.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

- Opioids
- Alcohol or
- Illicit drugs

Your doctor should:

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

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

Withdrawal: If you suddenly stop taking TEVA-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 TEVA-CLONAZEPAM or changing your medicine**

TEVA-CLONAZEPAM with Opioids: Taking TEVA-CLONAZEPAM 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 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 TEVA-CLONAZEPAM.
- Your risk of going through withdrawal is higher if you are taking TEVA-CLONAZEPAM for a long time or at high doses. However, symptoms can still occur if you are taking TEVA-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 heart rate 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 TEVA-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

TEVA-CLONAZEPAM with Opioids: Taking TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM
- TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM affects you. This effect of TEVA-CLONAZEPAM 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 TEVA-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
- Benzodiazepines such as TEVA-CLONAZEPAM are not recommended for the primary treatment of psychotic illness.
- Memory loss may occur when TEVA-CLONAZEPAM 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)

IMPORTANT: PLEASE READ

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/>

- TEVA-CLONAZEPAM 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 clonazepam have had thoughts of harming or killing themselves. If at any time you have these thoughts, contact your doctor immediately.

BEFORE you use TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM. 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 TEVA-CLONAZEPAM or may affect how well TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM.

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

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

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 30 kg)	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.

IMPORTANT: PLEASE READ

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 the 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:

If you think you, or a person you are caring for, have taken too much TEVA-CLONAZEPAM, contact a healthcare professional, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Take the missed dose of TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM 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 TEVA-CLONAZEPAM.

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 TEVA-CLONAZEPAM 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 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			√ (Immediately)

Serious side effects and what to do about them				
	in the mouth or eyes)			
	Depression. Symptoms may include: difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, 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.			√

Serious side effects and what to do about them				
	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): loss of consciousness with uncontrollable shaking		√	

Serious side effects and what to do about them

	<p>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.</p>			
--	--	--	--	--

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

HOW TO STORE IT

- Clonazepam tablets should be stored in tightly closed, light-resistant containers at 15–30°C.
- 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.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

If you want more information about TEVA-CLONAZEPAM:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer’s website <http://www.tevacanada.com>; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by:
 Teva Canada Limited
 30 Novopharm Court
 Toronto, Ontario
 M1B 2K9
 Canada

Last revised: December 7, 2021