PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

T\C PRO-OXAZEPAM

Oxazepam Tablets, Mfr. Std.

Tablets, 10 mg, 15 mg and 30 mg, Oral

Manufacturer's Standard

Anxiolytic-Sedative

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

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS, 1.2 Geriatrics	02/2023
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	02/2023
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PRO-OXAZEPAM (oxazepam tablets) is indicated for the short-term symptomatic relief of excessive anxiety and tension in patients with anxiety neurosis.

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

PRO-OXAZEPAM also is indicated for relieving the symptoms of acute alcoholic withdrawal, including acute agitation and impending delirium tremens.

1.1 Pediatrics

Pediatrics (<18 years of age): PRO-OXAZEPAM is contraindicated in infants (see 2 CONTRAINDICATIONS).

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies and experiences suggests that use in the geriatric population is associated with differences in safety or effectiveness. Long-term use of PRO-OXAZEPAM should be avoided in elderly patients. Enhanced monitoring is recommended (see 4.1 Dosing considerations, 7 WARNING AND PRECAUTIONS, Falls and Fractures).

2 CONTRAINDICATIONS

PRO-OXAZEPAM is contraindicated in:

- patients with previous history of hypersensitivity reactions to oxazepam, to other benzodiazepines or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING.
- infants
- patients with a history of glaucoma
- patients with myasthenia gravis

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

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

Withdrawal

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

- Avoid abrupt discontinuation or rapid dose reduction of PRO-OXAZEPAM.
- Terminate treatment with PRO-OXAZEPAM 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-OXAZEPAM 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-OXAZEPAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- PRO-OXAZEPAM 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.

- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of PRO-OXAZEPAM should be avoided in elderly patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

Adults: The recommended dosage is 30-120 mg daily, in divided doses, according to severity of symptoms and patient response. Initiate treatment by lower dose and increase gradually.

Elderly and/or Debilitated Patients: The recommended dosage is 5 mg once or twice daily, as tolerated. Initiate treatment always by the lowest dose and increase gradually as needed and tolerated.

Pediatrics: PRO-OXAZEPAM is contraindicated in infants (see 2 CONTRAINDICATIONS). Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

Dosage Adjustment

As with other benzodiazepines, the dosage of PRO-OXAZEPAM must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. As with other anxiolytic-sedatives, short courses of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without re-assessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of the drug should be provided, and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to short courses of therapy.

4.4 Administration

Patients should be advised to take the recommended dose orally with a glass of water. The tablets are scored therefore can be split adequately to deliver fractional doses if needed in the dosage.

4.5 Missed Dose

If the patient misses a dose, inform the patient to take it as soon as possible. However, if it is almost time for the next dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule. Inform the patient to not double doses.

5 OVERDOSAGE

Symptoms of overdosage with PRO-OXAZEPAM include somnolence, muscle weakness, ataxia, dysarthria and particularly in children, paradoxical excitement may occur. In more severe cases, diminished reflexes, confusion and coma may ensue. Fatalities rarely occur except when other drugs, alcohol or aggravating factors are involved. Hypotension and respiratory depressions are not found frequently unless other drugs have been associated.

There is no specific antidote. Management consists of supportive measures and close supervision and monitoring. Cardiovascular and central nervous system stimulants may be used, if necessary. Although oxazepam has a relatively long half-life, the use of dialysis is of questionable value.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets, 10 mg, 15 mg	D&C Yellow #10 Aluminum Lake, FD&C Yellow #6 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and starch.
	Tablets, 30 mg	Lactose, magnesium stearate, microcrystalline cellulose and starch.

PRO-OXAZEPAM 10 mg tablets are supplied as light yellow, round, flat-faced tablet with “R” score “10” on one side and plain on the other side. PRO-OXAZEPAM 10 mg tablets are supplied in bottles of 500.

PRO-OXAZEPAM 15 mg tablets are supplied as yellow, round, flat-faced tablet with “R” score “15” on one side and plain on the other side. PRO-OXAZEPAM 15 mg tablets are supplied in bottles of 500.

PRO-OXAZEPAM 30 mg tablets are supplied as white, round, flat-faced tablet with “R” score “30” on one side and plain on the other side. PRO-OXAZEPAM 30 mg tablets are supplied in bottles of 500.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Concomitant use with opioids: Concomitant use of benzodiazepines, including PRO-OXAZEPAM, 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; 9.1 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 central nervous system (CNS) depressant drugs with benzodiazepines.

If a decision is made to prescribe PRO-OXAZEPAM 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-OXAZEPAM than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking PRO-OXAZEPAM , 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-OXAZEPAM is used with opioids.

Advise patients not to drive or operate heavy machinery.

Dependence/Tolerance

Use of benzodiazepines, such as PRO-OXAZEPAM , 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 PRO-OXAZEPAM 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 PRO-OXAZEPAM . In individuals prone to substance use disorder, PRO-OXAZEPAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- PRO-OXAZEPAM 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-OXAZEPAM , 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 symptom, 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; Withdrawal; 4.1 Dosing Considerations)

Driving and Operating Machinery

Since patients may become excessively sedated or drowsy while taking PRO-OXAZEPAM , they should be warned not to undertake activities requiring mental alertness, judgment and physical coordination, such as driving or operating machinery, particularly in the early phases of dosage adjustment or with concomitant use of an opioid.

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.

Hepatic/Biliary/Pancreatic

Caution should be employed when PRO-OXAZEPAM , is administered to patients with impaired hepatic function, and blood counts and liver function tests should be performed regularly in patients receiving large doses or therapy for a prolonged period.

Immune

Hypersensitivity and Severe Anaphylactic Reactions: Skin rash, urticaria and rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including PRO-OXAZEPAM . Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop these symptoms after treatment with PRO-OXAZEPAM should not be rechallenged with the drug.

Neurologic

Seizures: Since oxazepam may occasionally exacerbate grand mal seizures, caution is required when it is used in epileptic patients and an adjustment may be necessary in their anticonvulsive medication. Abrupt withdrawal of PRO-OXAZEPAM in these patients should be avoided.

Psychiatric

Emotional Disorders: PRO-OXAZEPAM is not recommended in severely depressed patients. Caution is required in the treatment of patients with evidence of depression who may develop suicidal tendencies. PRO-OXAZEPAM should not be used in patients with non-pathologic anxiety with characterological and personality disorders or those with obsessive-compulsive neurosis.

Psychosis: PRO-OXAZEPAM is not recommended in psychotic patients. May react with excessive stimulation when treated with this drug, and PRO-OXAZEPAM should not be used in patients suspected of having a psychotic underlay to their anxiety.

Renal

Caution should be employed when PRO-OXAZEPAM , is administered to patients with impaired renal function.

Reproductive Health: Female and Male Potential

- **Fertility**

The clinical data for the effect of oxazepam on fertility is not available.

- **Teratogenic Risk**

There are no adequate and well-controlled studies of oxazepam in pregnant women. Animal studies with other anxiolytic-sedative agents have suggested increased risk of congenital malformations (see 7.1.1 Pregnant women; 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

Several studies have suggested increased risk of congenital malformations associated with the use of anxiolytic-sedative agents such as diazepam, chlordiazepoxide and meprobamate during the first trimester of pregnancy. Oxazepam, a benzodiazepine derivative, has not been studied adequately to determine whether it too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

7.1.2 Breast-feeding

It is unknown if oxazepam is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): PRO-OXAZEPAM is contraindicated in infants (see 2 CONTRAINDICATIONS).

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment).

7.1.4 Geriatrics

Geriatrics (>65 years of age): Long-term use of PRO-OXAZEPAM 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

As with other benzodiazepines, adverse reactions most observed include drowsiness, dizziness, fatigue and ataxia.

Other adverse reactions reported are headache, vertigo, diplopia, blurred vision, weakness, hypotension, impairment of memory, slurred speech, sluggish response, hypoactivity, dysarthria, depression, euphoria, anorexia, nausea, constipation, incontinence or urinary retention, changes in libido, urticaria, skin rashes, generalized exfoliative dermatitis, tremors, edema and changes in the EEG pattern (increased fast activity).

Drug dependence after withdrawal, abstinence symptoms such as anxiety, muscle twitches, convulsions or delirium with psychotic manifestations may occur (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

Release of hostility and other paradoxical reactions such as irritability, excitability, rage, hallucination, increased muscle spasticity and sleep disturbances may occur with PRO-OXAZEPAM . Leukopenia, jaundice, hypersensitivity reactions and abnormal kidney and liver function tests have been reported with this class of drugs (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; Renal).

8.5 Post-Market Adverse Reactions

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 (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).

Dependence/Withdrawal

Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as PRO-OXAZEPAM . Severe and life-threatening symptoms have been reported (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependance/Tolerance).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of PRO-OXAZEPAM 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk form Concomitant use with Opioids; 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with Opioids).

9.2 Drug Interactions Overview

Benzodiazepines, including PRO-OXAZEPAM , may produce additive CNS depressant effects when co-administered with alcohol, and medications, including opioids, which themselves can produce CNS depression (see 9.3 Drug-Behavioural Interactions; 9.4 Drug-Drug Interactions).

The activity of benzodiazepines, including PRO-OXAZEPAM , may be enhanced by compounds which inhibit certain hepatic enzymes such as cytochrome P450 enzymes (see 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Benzodiazepines, including PRO-OXAZEPAM , may produce additive CNS depressant effects when co-administered with alcohol.

9.4 Drug-Drug Interactions

CNS depressant drugs: Benzodiazepines, including PRO-OXAZEPAM , may produce additive CNS depressant effects when co-administered sedative antihistamines, narcotic analgesics, anticonvulsants, antipsychotics (neuroleptics), anesthetics, antidepressant agents or psychotropic medications which themselves can produce CNS depression.

Cytochrome P450: Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Examples include cimetidine or erythromycin.

Opioids: Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including PRO-OXAZEPAM , 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risk from Concomitant use with Opioids; 7 WARNINGS AND PRECAUTIONS, General, Concomitant use with Opioids)

9.5 Drug-Food Interactions

Interactions with food have not been established.

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

Oxazepam, a benzodiazepine, is a CNS depressant. Oxazepam possesses anxiolytic and sedative properties of value in the symptomatic relief of manifest anxiety and tension states in psychoneurotic patients.

10.2 Pharmacodynamics

Oxazepam is a benzodiazepine derivative with a wide spectrum of pharmacological effects upon the CNS, qualitatively similar to chlordiazepoxide and diazepam, but less potent.

10.3 Pharmacokinetics

Absorption and Distribution

Following an oral dose, peak plasma levels of oxazepam are reached in 3-4 hours and its half-life is estimated to be approximately 11 hours. Plasma binding of oxazepam in normal subjects is approximately 89%.

Metabolism

Oxazepam is conjugated to a pharmacologically inactive glucuronide.

Elimination

Excretion is primarily in the urine, as the glucuronide, with the feces containing approximately 21% of unchanged drug. After the administration of a single oral dose, most of the drug is excreted within 48 hours.

Special Populations and Conditions

- **Geriatrics:** Age does not appear to have a clinically significant effect on oxazepam kinetics. A statistically significant increase in elimination half-life in the very elderly (>80 years of age) as compared to younger subjects has been reported, due to 30% increase in volume distribution, as well as a 50% reduction in unbound clearance of oxazepam in the very elderly.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15 to 30°C.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

None

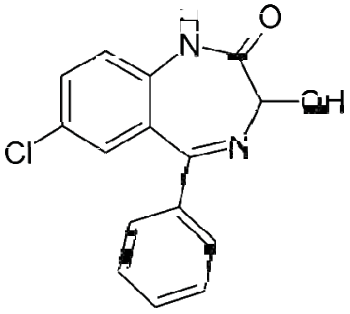
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Oxazepam
Chemical name:	7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-l1,4-benzodiazepin-2 one
Molecular formula and molecular mass:	$C_{15}H_{11}ClN_2O_2$ 286.71 g/mol

Structural formula:



Physicochemical properties:

Description:	White to pale yellow powder or crystalline solid, practically odourless with bitter taste. Melting point: 205-206°C
Solubility:	Soluble in alcohol, chloroform, dioxane. Solubility in water: 0.02 g/L at 22°C
Log K_{OW}:	2.24 at pH 7.4
pH:	Between 4.8 and 7.0 (1 in 50 Suspension)

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity: The oral LD_{50} in mice and rats, is greater than 5000 mg/kg.

Subacute Toxicity: Fatty metamorphosis of the liver occurred in rats in six-week studies with oxazepam administered in the diet at 0.5%. No liver necrosis or fibrosis occurred. Dogs were treated for 4 weeks with doses of 480 and 960 mg/kg p.o. Two out of eight dogs at the high dose died with evidence of circulatory collapse.

Chronic Toxicity: Oxazepam was administered to rats in the diet at levels of 0, 0.015, 0.03, 0.06 and 0.12% in a 55-56 week study. Increase in the organ-body weight ratio were seen for the liver at the 3 upper levels (0.03, 0.06 and 0.12%). An increase in kidney weight occurred in males at the two upper levels. The changes were considered reversible.

Reproductive and Developmental Toxicology:

In mice, reproduction studies in which oxazepam was administered orally at doses of 25, 50 and 100 mg/ kg/day on days 7 through 14 of the gestation periods showed no effect on mortality, litter size and in the number of deaths of the young in the first few days after birth.

In rats on two consecutive matings, the percent of females conceiving and giving birth to viable young was 50% and 55% compared to an average of 87.5% for the controls, when oxazepam was administered in the diet at 0.06%. The average litter size for this same group for the two phases was 9.8 and 11.6 and 11.9 for controls. No gross abnormalities were detected in the offspring.

17 SUPPORTING PRODUCT MONOGRAPHS

1. OXPAM® (oxazepam), tablets, 10 mg, 15 mg, 30 mg, submission control 248567, Product Monograph, Biomed Pharma (May 17, 2022)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

T/C PRO-OXAZEPAM

Oxazepam Tablets, Mfr. Std.

Read this carefully before you start taking **PRO-OXAZEPAM** 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-OXAZEPAM** .

Serious Warnings and Precautions

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

- **opioids,**
- **alcohol, or**
- **illicit drugs.**

Your healthcare professional should:

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

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

Withdrawal: If you suddenly stop taking PRO-OXAZEPAM , lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about).

- **Always contact your healthcare professional before stopping or lowering your dose of PRO-OXAZEPAM or changing your medicine.**

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

- **severe drowsiness,**
- **decreased awareness,**
- **breathing problems,**
- **coma,**
- **death.**

What is PRO-OXAZEPAM used for?

PRO-OXAZEPAM is used in adults to relieve:

- short-term anxiety and tension from anxiety neurosis (a type of anxiety); and
- symptoms of sudden alcohol withdrawal (e.g., agitation and mental status changes).

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

How does PRO-OXAZEPAM work?

PRO-OXAZEPAM belongs to the group of medicines called benzodiazepines, which are Central Nervous System (CNS) depressants. It affects certain substances in your brain called neurotransmitters to reduce symptoms caused by anxiety and stress.

What are the ingredients in PRO-OXAZEPAM ?

Medicinal ingredient: Oxazepam.

Non-medicinal ingredients: D&C Yellow #10 Aluminum Lake (10 mg and 15 mg only), FD&C Yellow #6 Aluminum Lake (10 mg and 15 mg only), lactose, magnesium stearate, microcrystalline cellulose and starch.

PRO-OXAZEPAM comes in the following dosage forms:

Tablets: 10 mg, 15 mg and 30 mg of oxazepam.

Do not use PRO-OXAZEPAM if:

- you are allergic to benzodiazepines, such as oxazepam, or to any other ingredient in PRO-OXAZEPAM ;
- you are under 12 months of age;
- you have a history of glaucoma (increased pressure in your eye causing damage to the optic nerve); and
- you have myasthenia gravis (a condition characterized by weakness of your muscles used for movement).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PRO-OXAZEPAM . Talk about any health conditions or problems you may have, including if you :

- 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).
- are 65 years of age or older.
- have or have had a mental health disorder (e.g., psychosis, personality disorder and obsessive-compulsive disorder).
- have depression or signs of depression.
- have a condition that causes weakness or frailty.

- have liver problems.
- have kidney problems.
- are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed.
- drink or plan to drink alcohol. Do NOT drink alcohol while you take PRO-OXAZEPAM .
- unable to digest some milk sugars (e.g., lactose intolerance). PRO-OXAZEPAM contains the milk sugar lactose.

Other warnings you should know about:

Severe Allergic Reaction: In rare cases, benzodiazepines like PRO-OXAZEPAM have caused severe allergic reactions including anaphylaxis, which can be life-threatening. The symptoms of a severe allergic reaction include angioedema of the tongue or throat (swelling of tissues under the skin), shortness of breath, throat closing, nausea or vomiting. Angioedema can lead to a blocked airway and can be life- threatening. If you develop angioedema or you notice signs of a severe allergic reaction after taking PRO-OXAZEPAM , you should stop taking PRO-OXAZEPAM and tell your 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 symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop PRO-OXAZEPAM .

Your risk of going through withdrawal is higher if you are taking PRO-OXAZEPAM for a long time or at high doses. However, symptoms can still occur if you are taking PRO-OXAZEPAM 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 healthcare professional **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 behavior 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 healthcare professional before stopping or reducing your dose of PRO-OXAZEPAM or changing medications.

- always follow your healthcare professional's instructions on how to reduce your dose carefully and safely.
- tell your healthcare professional **right away** if you experience any unusual symptoms after changing or stopping your treatment.

PRO-OXAZEPAM with Opioids: Taking PRO-OXAZEPAM with opioid medicines can cause severe drowsiness and breathing problems.

Tell your healthcare professional if you:

- are taking opioid medicines.
- are prescribed an opioid medicine after you start taking PRO-OXAZEPAM .

Driving and Using Machines: Do NOT drive or operate heavy machinery or do tasks that require special attention while taking PRO-OXAZEPAM . This is especially important if you are taking other depressants like an opioid medicine.

Falls and Fractures: Benzodiazepines like PRO-OXAZEPAM can cause you to feel sleepy, dizzy and affect your balance. This increases your 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.

Monitoring and Testing: Your healthcare professional may conduct blood tests to assess your health, especially at the start of your treatment. Your healthcare professional will interpret your results and may adjust or stop your dose of PRO-OXAZEPAM .

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

Serious Drug Interactions

Taking PRO-OXAZEPAM and opioids may cause:

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

The following may interact with PRO-OXAZEPAM :

- alcohol. Do not take PRO-OXAZEPAM if you drink alcohol;
- medicines used to treat allergies such as, sedative antihistamines;
- medicines used to prevent or treat seizures (anticonvulsants);
- medicines used to produce a local or general loss of sensation, including pain (anesthetics);
- medicines used to treat depression (antidepressants);
- medicines used to treat mental health disorders or change your mental state or mood (antipsychotic and psychotropic medications);

- medicines that inhibit certain liver enzymes, particularly cytochrome P450 (e.g., cimetidine and erythromycin). If you are unsure, talk to your healthcare professional;
- other benzodiazepines typically used to treat anxiety, insomnia and seizures.

DO NOT USE PRO-OXAZEPAM along with other medications without first discussing this with your healthcare professional.

How to take PRO-OXAZEPAM :

- Take PRO-OXAZEPAM exactly as prescribed by your healthcare professional.
- You should take PRO-OXAZEPAM with a glass of water.
- Do not consume any alcohol while taking PRO-OXAZEPAM .
- Always follow your healthcare professional's instructions on how to lower and stop your dose carefully. This helps to avoid unwanted effects. However, if you notice any signs or symptoms of withdrawal, tell your healthcare professional right away.

Usual dose:

Your healthcare professional will determine the right dose and the length of PRO-OXAZEPAM treatment for you. This will depend on your age, current health, and if you take certain other medications. They may also adjust your dose to ensure that the lowest effective dose is prescribed.

Overdose:

Symptoms of an overdose with PRO-OXAZEPAM include:

- drowsiness,
- muscle weakness,
- loss of coordination,
- speaking problems,
- abnormal movements (paradoxical excitement),
- slower reflexes,
- confusion,
- coma,
- low blood pressure,
- breathing difficulties.

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

Missed Dose:

If you forget or miss a dose of PRO-OXAZEPAM , do not take the missed dose. Instead, take the next scheduled dose at the usual time. Do not try to make up for the missed dose by taking a double dose.

What are possible side effects from using PRO-OXAZEPAM ?

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

Side effects of PRO-OXAZEPAM include:

- falls and fractures,
- drowsiness,
- dizziness,
- fatigue,
- difficulties with coordination,
- slow response,
- headache,
- vertigo,
- blurred or double vision,
- weakness,
- memory loss,
- reduced activity or lack of energy,
- speech problems,
- a feeling or state of intense excitement and happiness,
- anorexia (an eating disorder characterized by not eating or loss of appetite),
- nausea,
- constipation,
- urinating difficulties,
- changes in sex drive (libido),
- anxiety,
- uncontrollable shaking, muscle twitches or spasms.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get medical help**
	Only if severe	**In all cases**	
RARE			
Severe allergic reaction: fever, skin rash, hives, itching, swelling of the eyelids, face, lips, tongue or throat, trouble breathing, wheezing, nausea, chest pain, chest tightness, or vomiting.			✓
UNKNOWN FREQUENCY			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
Respiratory depression: slow, shallow or weak breathing.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get medical help**
	Only if severe	**In all cases**	
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond. **Delirium tremens:** severe confusion, shivering, irregular heart rate and excessive sweating. **Feeling depressed** **Dissociation:** feeling disconnected from reality. **Hallucinations:** seeing or hearing things that are not there. **Mania:** overactive behaviour and thoughts. **Psychosis:** believing in things that are not true**.** **Convulsions:** (seizures – including some that do not stop): loss of consciousness **with uncontrollable shaking.** **Thoughts or actions of suicide** **Other symptoms 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.		✓	
Edema: unusual swelling of the arms, hands, legs, feet and ankles, face, or airway passages.			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get medical help**
	Only if severe	**In all cases**	
Skin disorders: rash, blistering, itching all over the body, reddening of the skin, itchy red spots, swelling of eyelids, face or lips, peeling, or lost skin.			✓
Jaundice (build up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool, or itching all over your body.			✓
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up).		✓	
Depression (sad mood that won't go away): difficulty sleeping, 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), thoughts of death, or thoughts of suicide.		✓	
Leukopenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms.		✓	

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-OXAZEPAM between 15°C and 30°C.

Keep PRO-OXAZEPAM in a safe place out of reach and sight of children.

If you want more information about PRO-OXAZEPAM:

- 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 the sponsor Pro Doc Ltée at 1-800-361-8559, www.prodoc.qc.ca or medinfo@prodoc.qc.ca

This leaflet was prepared by Pro Doc Ltée.

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