PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

DIAZEPAM INJECTION USP

Diazepam

Sterile Solution for Injection, 5 mg/mL, Intramuscular and Intravenous Injection Only

USP Standard

Anxiolytic–Sedative

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Diazepam Injection USP (diazepam) is indicated when a rapid response to the use of diazepam isdesired and may be useful:

- To control prolonged seizure activity (status epilepticus) not associated with acute neurologicdisorders.
- To alleviate the symptoms of acute alcoholic withdrawal, including delirium tremens.
- In acute anxiety or tension states related to non-psychotic emotional disorders and to relievespasticity in cerebral palsy, athetosis and the rare "Stiff Man Syndrome".

1.1 Pediatrics

Pediatrics (≥ 12 years of age): Based on the data submitted and reviewed by Health Canada, the safetyand efficacy of Diazepam Injection USP in pediatric patients has not been established in children under12; therefore, Health Canada has not authorized an indication for children under 12. Diazepam Injection USP is contraindicated in infants.

1.2 Geriatrics

Long-term use of Diazepam Injection USP should be avoided in elderly patients. Enhanced monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS, Falls and fractures; 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing considerations).

2 CONTRAINDICATIONS

Diazepam Injection USP is contraindicated in:

- patients with known hypersensitivity to benzodiazepines, to this drug or to any ingredient in theformulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- myasthenia gravis,
- acute narrow angle glaucoma,
- infants

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse
The use of benzodiazepines, including Diazepam Injection USP, 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 Diazepam Injection USP

- Monitor all patients regularly for the development of these behaviours or conditions.
- Diazepam Injection USP should be stored securely to avoid theft or misuse.

Withdrawal
Benzodiazepines, like Diazepam Injection USP, can produce severe or life-threatening withdrawalsymptoms.

- Avoid abrupt discontinuation or rapid dose reduction of Diazepam Injection USP.
- Terminate treatment with Diazepam Injection USP 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 Diazepam Injection USP and opioids may result in profound sedation, respiratorydepression, 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 alternativetreatment 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

- Diazepam Injection USP should always be prescribed at the lowest effective dose for the shortestduration possible.
- Diazepam Injection USP 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 patientswith a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raisingthe 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 Diazepam Injection USP should be avoided in elderly patients. Enhancedmonitoring is recommended.
- Diazepam should not be administered to patients in shock or coma.

4.2 Recommended Dose and Dosage Adjustment

Diazepam Injection USP is used without diluent for both the IM and the IV routes. The intramuscularroute should be preferred whenever the indication and urgency of the clinical situation permit.

While the dosage should be individualized for maximum beneficial effect, as a general rule the meandose for both the IV and IM routes is:

	USUAL DOSAGE
1. Status epilepticus including severe recurrent seizures: For the control of prolonged seizure activity.	5 to 10 mg IV (preferred route) or IM initially. Repeat in 2 to 4 hours, if necessary.
2. Acute alcoholic withdrawal: To alleviate the symptoms of acute alcoholic withdrawal including delirium tremens.	10 mg IM or IV initially, then 5 mg to 10 mgin 3 to 4 hours, if necessary.
3. Acute anxiety related to stressful conditions or non-psychotic emotional disorders.	2 mg to 10 mg IM or IV. Repeat in 3 to 4hours, if necessary.
4. For the relief of muscle spasm in cerebral palsy athetosis, the rare "Stiff Man Syndrome" and adjunctively in tetanus.	5 mg to 10 mg IM or IV initially, then 5 mg to10 mg in 3 to 4 hours, if necessary. For tetanus, larger doses may be required.
Pediatrics (≥ 12 years of age):	Diazepam Injection USP is not indicated in children under 12 years of age, and is contraindicated in infants.
Elderly and debilitated patients: (See 7 WARNINGS and PRECAUTIONS, 7.1 Special Populations, 7.1.4 Geriatrics)	2 mg to 5 mg IM or IV

In acute conditions, the injection may be repeated within one hour although an interval of three to four hours is usually satisfactory. Generally not more than 30 mg should be given in an eight-hour period.

4.4 Administration

Intramuscular: Diazepam Injection USP should be injected deeply into the muscle.

Intravenous: Diazepam Injection USP should be administered slowly, i.e. 5 mg (1 mL) per minute.

- Rapid injection or the use of veins with too small a lumen carries the risk of thrombophlebitis. Intravenous injection should be directly into a large lumen vessel, such as an antecubital vein, andthe ampoule solution should be administered slowly, e.g. 1 mL (5 mg) per minute. Do not mix or dilute Diazepam with other solutions or drugs.
- Intra-arterial injection must be carefully avoided on account of the danger of necrosis.
- Diazepam should not be added to parenteral fluids. Neither should it be further diluted or mixedwith other drugs.

5 OVERDOSAGE

The main symptoms of overdosage are drowsiness, oversedation and ataxia. When the effects of the drug overdosage begin to wear off, the patient exhibits some jitteriness and overstimulation. The cardinal manifestations of overdosage are drowsiness and confusion, reduced reflexes and coma. Thereare minimum effects on respiration, pulse and blood pressure unless the overdosage is extreme.

There is no specific antidote known. If necessary, a CNS stimulant such as caffeine or methylphenidatemay be administered with caution. Supportive measures should be instituted as

indicated: maintenance of an adequate airway, levarterenol bitartrate or metaraminol for hypotension. Dialysis appears to be of little value.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular, Intravenous	Sterile Solution for Injection / 5 mg/mL	anhydrous ethyl alcohol 10%, propylene glycol 40%, sodium hydroxide toadjust pH and water for injection.

Diazepam Injection USP 5 mg/mL is available in 2 mL ampoules, boxes of 10.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Concomitant use with opioids:

Concomitant use of benzodiazepines, including Diazepam Injection USP, 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 DRUG INTERACTIONS, 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 CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe Diazepam Injection USP 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 Diazepam Injection USP than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking Diazepam Injection USP, 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 Diazepam Injection USP 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.

Alertness:

After parenteral administration of diazepam injectable, ambulation should be delayed at least one or two hours or until complete alertness is restored.

Patients receiving diazepam injectable should be advised to proceed cautiously wherever mental alertness and physical coordination are required.

Dependence/Tolerance

Use of benzodiazepines, such as Diazepam Injection USP, 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 Diazepam Injection USP 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 Diazepam Injection USP. In individuals prone to substance use disorder, Diazepam Injection USP should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- Diazepam Injection USP 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 Diazepam Injection USP, 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 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; 4 DOSAGE AND ADMINISTRATION, 4.1 Dosing Considerations)

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hepatic/Biliary/Pancreatic

The usual precautions in treating patients with impaired hepatic functions should be observed. If diazepam injectable is administered for protracted periods, periodic blood counts and liver function tests may be advisable.

Monitoring and Laboratory Tests

Interference with Serum Creatine Phosphokinase Determinations: As with a number of other intramuscular dosage forms, intramuscular administration of diazepam injectable (but not oral or intravenous administration) can lead to a rise in serum creatine phosphokinase activity. A maximum level is usually noticed between 12 and 24 hours after intramuscular injection. These elevated readings should be taken into account in the event of differential diagnosis of myocardial infarction.

Musculoskeletal 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.

Neurologic

Use in Status Epilepticus: Diazepam is not recommended as a substitute for standard anticonvulsant medication in the long-term control of epilepsy. Appropriate anticonvulsant therapy should be instituted or continued when necessary, as soon as possible after interruption of the status epilepticus. Although diazepam injectable is used to control status epilepticus, it may occasionally induce or aggravate seizures in some patients with convulsive disorders.

Psychiatric

Use in Emotional Disorders: Diazepam is not recommended in the treatment of psychotic or severely depressed patients. Precautions are indicated for severely depressed patients or those who show any evidence of impending depression, particularly the recognition that suicidal tendencies may be present

and protective measures may be necessary.

Since excitement and other paradoxical reactions may result from use of the drug in psychotic patients, it should not be used in ambulatory patients suspected of having psychotic tendencies.

Respiratory

Rare reports of apnea or cardiac arrest have been noted, usually following IV administration, especiallyin elderly or very ill patients and those with limited pulmonary reserve. Duration is generally brief. Resuscitative facilities should be available since lingual obstruction of the airway may occur, particularly in children and in the elderly; caution is required to maintain a free airway in patientsreceiving Diazepam.

Renal

The usual precautions in treating patients with impaired renal functions should be observed.

Reproductive Health: Female and Male Potential

- Fertility

This information is not available for this drug product.

- Teratogenic Risk

This information is not available for this drug product.

7.1 Special Populations

7.1.1 Pregnant Women

Diazepam should not be used during the first trimester of pregnancy except if absolutely necessary.The safety and efficacy of diazepam injectable in obstetrics have not yet been established.

In humans, comparable blood levels of diazepam were obtained in maternal and cord blood indicatingrapid placental transfer of the drug following parenteral administration.

7.1.2 Breast-feeding

It is unknown if Diazepam Injection USP is excreted in human milk. Precaution should be exercisedbecause many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (≥ 12 years of age): The safety and efficacy of diazepam injectable have not been establishedin children under 12. Diazepam injection USP is contraindicated in infants.

7.1.4 Geriatrics

Elderly and debilitated patients and those with organic brain disorders have been found to be very prone to central nervous system depression following even low doses of diazepam. For these patients,diazepam injectable should be used with caution and in low doses to preclude development of ataxia, sedation or other possible adverse effects.

Long-term use of Diazepam Injection USP should be avoided in elderly or debilitated patients who maybe 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

The most common adverse reactions reported for diazepam injectable are drowsiness and ataxia.

Other reactions noted less frequently are fatigue, dizziness, nausea, blurred vision, diplopia, vertigo, headache, slurred speech, tremors, hypoactivity, dysarthria, euphoria, impairment of memory, confusion, depression, incontinence or urinary retention, constipation, skin rash, generalized exfoliativedermatitis, hypotension, tachycardia, flushing, hematuria, changes in libido, pain at the site of injection and phlebitis following intravenous administration.

The more serious adverse reactions occasionally reported are leucopenia, jaundice, hypersensitivityand paradoxical reactions. Circulatory and respiratory depression may follow rapid intravenous administration of diazepam injectable.

Paradoxical reactions such as hyperexcited states, anxiety, excitement, hallucinations, increased muscle spasticity, insomnia, rage, as well as sleep disturbances and stimulation have been reported, should these occur, the drug should be discontinued.

Minor changes in EEG patterns have been observed in patients on diazepam injectable therapy. These changes consist of low to moderate voltage fast activity, 20-30 cycles per second, and are of no known significance.

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.

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

Concomitant use of Diazepam Injection USP and opioids may result in profound sedation, respiratorydepression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternativetreatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation. (see 7 WARNINGS AND PRECAUTIONS, General, Risks from Concomitant use with Opioids)

9.2 Drug Interactions Overview

Potentiation of Drug Effects: Careful consideration should be given if diazepam injectable is to be combined with other psychotropic agents (phenothiazines, barbiturates, MAO inhibitors and other antidepressants) because the pharmacological action of these agents might potentiate the action ofdiazepam injectable.

Patients should be advised to abstain from alcohol during treatment with diazepam injectable.

In view of possible adverse reactions and potentiation of effects, patients should be advised to abstainfrom CNS depressant drugs during treatment with diazepam injectable.

9.3 Drug-Behavioural Interactions

Use of benzodiazepines, such as Diazepam Injection USP, can lead to abuse, misuse, addiction, physicaldependence (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 (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

9.4 Drug-Drug Interactions

Concomitant use of Diazepam Injection USP and opioids may result in profound sedation, respiratory depression, coma and death. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of Diazepam Injection USP and other CNS depressant drugs. (see 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

Interference with Serum Creatine Phosphokinase Determinations: As with a number of other intramuscular dosage forms, intramuscular administration of diazepam injectable (but not oral or intravenous administration) can lead to a rise in serum creatine phosphokinase activity. A maximum level is usually noticed between 12 and 24 hours after intramuscular injection. These elevated readingsshould be taken into account in the event of differential diagnosis of myocardial infarction (see 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Diazepam is an anxiolytic-sedative drug useful in the symptomatic relief of anxiety and tension states associated with psychoneurotic disorders. It also has anticonvulsant properties and adjunctive value inthe relief of certain neurospastic conditions. As an anticonvulsant, diazepam injectable has a major usein the control of status epilepticus.

Peak blood levels are reached very rapidly after intravenous administration of diazepam as compared to one hour after a single oral dosing and are of the same magnitude. The acute half-life is 2-3 hours with a slower decline thereafter, possibly due to tissue storage. Repeated doses further

increase blood levels.

10.2 Pharmacodynamics

Diazepam is a benzodiazepine with CNS depressant properties and a somewhat flatter dose-response slope than the sedative-hypnotic drugs. In laboratory animals it produces, in varying doses, taming, disinhibitory, sedative, anticonvulsant, muscle relaxant, ataxic hypnotic effects.

As with the sedative-hypnotic drugs, at doses producing only mild sedation, it reduces slightly the behavioural arousal, increases responsiveness to environmental stimuli, suppresses passive avoidance behaviour and increases approach behaviour, while, at slightly higher doses, it appears to increase errors of commission in performing tasks and may produce drowsiness, muscle weakness and ataxia. The most selective behavioural properties observed in laboratory animals at low doses are suppression of passive avoidance behaviour and "trace" avoidance conditioning, blocking the extinction of active avoidance behaviour and increased food intake.

Diazepam selectively suppresses subcutaneous metrazol-induced convulsions, but is less effective against maximal electroshock convulsions and relatively ineffective against minimal electroshock convulsions. It reduces body tone in the cat at sub-ataxic doses and is active in the inclined screen test, and in blocking decerebrate rigidity and the spinal reflex in the cat at higher doses.

Parenteral administration decreases the amplitude of local evoked potentials recorded from the mesencephalic reticular formation, septal region, amygdaloid complex and hyppocampus in the cat andmonkey. It also depresses the cardiovascular and intestinal responses to stimulation of the hypothalamus in the cat.

Diazepam is relatively devoid of autonomic effects and does not significantly reduce locomotor activityat low doses, or depress amphetamine-induced excitation. In high doses it activates the drug metabolizing enzymes in the liver. Diazepam also possesses dependence liability and may produce withdrawal symptoms, but has a wide margin of safety against poisoning.

10.3 Pharmacokinetics

Metabolism studies in animals and man have indicated that oral diazepam is rapidly absorbed from thegastrointestinal tract. Peak blood levels are reached within 1 to 2 hours after administration. The acutehalf-life is 6 to 8 hours with a slower decline thereafter, possibly due to tissue storage.

With the parenteral form, peak blood levels are reached within 15 minutes after intravenous administration and are of the same magnitude as after oral administration. The respective half-life isapproximately 2 to 3 hours.

The distribution and fate of tritium-labelled diazepam in man has indicated that the drug has a rapid and extensive uptake by tissues. Although the radioactivity in blood appears to represent mainly theintact drug, diazepam was shown to be excreted exclusively in the form of its metabolites. The two major metabolites are oxazepam glucuronide and N-demethylated diazepam.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15 and 30 °C. Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

This information is not available for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

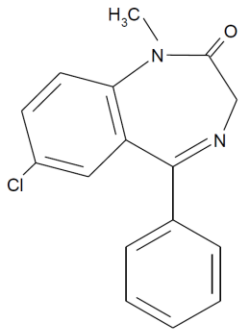
Drug Substance

Proper name: Diazepam

Chemical name: 7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Molecular formula and molecular mass: $C_{16}H_{13}ClN_2O$ 284.75 g / mol

Structural formula:



Diazepam

Physicochemical properties: Diazepam is a white to practically white crystalline powder, odorless. Practically insoluble in water.

Product Characteristics:

This information is not available for this drug product.

14 CLINICAL TRIALS

This information is not available for this drug product.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Administration Route	LD_{50} (mg/kg)	
	Mouse	**Rat**
Intravenous	24.9	51.8
Intramuscular	66.0	> 50

Administration Route	LD_{50} (mg/kg)	
	Mouse	**Rat**
Oral	1050	1050

Subacute Toxicity

Diazepam has been administered orally at 20, 80 and 320 mg/kg to male and female rats, for a 12-weekperiod.

Hematological and biochemical evaluations as well as urinalyses have been performed after 5 and 12weeks of treatment respectively.

Following 12 weeks of treatment, the animals were sacrificed and their tissues submitted to histopathological examination. These toxicity studies on diazepam gave results similar to thoseobtained with other diazepam preparations.

An increase in the size of the liver as well as hepatic degeneration have been observed following benzodiazepine administration.

Local Irritation:

Diazepam 0.1 mL was administered to rabbits twice daily for five consecutive days. The injections weremade in the marginal vein or one ear, the other ear being used as control. Local reactions such as temperature elevation, edema and erythema were observed, but these manifestations were transient and disappeared completely within 7 days of the last injection of diazepam.

17 SUPPORTING PRODUCT MONOGRAPHS

Diazepam Injection USP, Sterile Solution for Injection, 5 mg/mL, submission control 245324, Product Monograph, Sandoz Canada Inc. May, 12, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Diazepam Injection USP

Diazepam

Read this carefully before you start taking **Diazepam Injection USP** 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 **Diazepam Injection USP**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take Diazepam Injection USP as prescribed, you are at risk for abuse, misuse and addiction. This can result in overdose or death, especially if it is taken with:

- **opioids**
- **alcohol or**
- **illicit drugs**

Your doctor should:

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

Store Diazepam Injection USP in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking Diazepam Injection USP, 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 doctor before stopping, or lowering your dose of Diazepam Injection USP or changing your medicine.**

Diazepam Injection USP with Opioids: Taking Diazepam Injection USP with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**
- **coma**

- **death**

What is Diazepam Injection USP used for?

- Diazepam Injection USP is used to:
  - relieve anxiety,
  - control agitation caused by alcohol withdrawal and
  - control seizures
- It is also used to control muscle spasms and spasticity caused by certain neurological disorders such as
  - cerebral palsy,
  - athetosis (involuntary movements), and
  - stiff-man syndrome (body stiffness).

Diazepam Injection USP is not for use in children less than 12 years of age.

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

How does Diazepam Injection USP work?

Diazepam Injection USP works by calming the brain and nerves.

What are the ingredients in Diazepam Injection USP

Medicinal ingredients: Diazepam

Non-medicinal ingredients: anhydrous ethyl alcohol, benzoic acid, benzyl alcohol as preservative, propylene glycol, sodium hydroxide to adjust pH and water for injection..

Diazepam Injection USP comes in the following dosage forms:

Sterile Solution for Injection, 5 mg / mL

Do not use Diazepam Injection USP if:

- you are allergic to it; or to other benzodiazepines.
- you have a disorder of the nervous system that causes muscle weakness (myasthenia gravis).
- you have a serious eye condition that may cause loss of vision (narrow angle glaucoma). Diazepam Injection USP is not for use in children less than 12 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Diazepam Injection USP. 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)

Other warnings you should know about:

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 Diazepam Injection USP.

Your risk of going through withdrawal is higher if you are taking Diazepam Injection USP for a long time or at high doses. However, symptoms can still occur if you are taking Diazepam Injection USP as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behaviour and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always contact your doctor before stopping or reducing your dose of Diazepam Injection USP 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

Diazepam Injection USP with Opioids: Taking Diazepam Injection USP 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 Diazepam Injection USP

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and Diazepam Injection USP affects you.

Falls and Fractures: Benzodiazepines like Diazepam Injection USP 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

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

The following may interact with Diazepam Injection USP

Serious Drug Interactions

Taking Diazepam Injection USP and opioids may cause:

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

How to take Diazepam Injection USP:

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

Usual dose:

Diazepam Injection USP will be given by your health care professional who will determine your dose and the best way to give it to you.

Overdose:

Signs that you have taken too much Diazepam Injection USP include

- Drowsiness and confusion,
- reduced reflexes and
- loss of consciousness (coma).

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

What are possible side effects from using Diazepam Injection USP?

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

- Falls and fractures

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**	
UNKNOWN			
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rollingof 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 immediate medical help
	Only if severe	In all cases	
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannotmove or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnectedfrom reality **Hallucinations:** seeing or hearingthings that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things thatare not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicideOther** **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.		✓	

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 HealthCanada 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 toreport 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 between 15 and 30 °C. Protect from light.

Keep out of reach and sight of children.

If you want more information about Diazepam Injection USP

- 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 calling 1-800-656-0793.

This leaflet was prepared by TELIP, LLC, a subsidiary of Teligent, Inc.

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