

PRODUCT MONOGRAPH

 **APO-DIAZEPAM**

Diazepam Tablets, USP

2, 5 and 10 mg

Anxiolytic-sedative

**APOTEX INC.
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Toronto, Ontario
M9L 1T9**

Control #: 168021

**DATE OF REVISION:
June 5, 2014**

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APO-DIAZEPAM

Diazepam Tablets, USP

2, 5 and 10 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients
Oral	Tablet, 2 mg, 5 mg and 10 mg	Lactose monohydrate, microcrystalline cellulose, starch, magnesium stearate, D&C yellow #10 (5 mg only), FD&C yellow #6 (5 mg only), FD&C blue #1 (10 mg only) and FD&C blue #2 (10 mg only)

INDICATIONS AND CLINICAL USE

APO-DIAZEPAM (diazepam) is useful in the symptomatic management of mild to moderate degrees of anxiety in conditions dominated by tension, excitation, agitation, fear or aggressiveness, such as may occur in: psychoneurosis, anxiety reactions due to stress conditions and anxiety states with somatic expression.

In acute alcoholic withdrawal, APO-DIAZEPAM may be useful in the symptomatic relief of acute agitation, tremor and impending acute delirium tremens.

APO-DIAZEPAM is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology, such as inflammation of the muscle and joints or secondary to trauma; spasticity caused by upper motor neuron disorders, such as cerebral palsy and paraplegia; athetosis and the rare "stiff man syndrome".

Geriatrics: Elderly and debilitated patients are especially susceptible to dose-related adverse events and a reduced dose is recommended (see WARNING AND PRECAUTIONS, Special Population, Geriatrics and DOSAGE AND ADMINISTRATION, Dosing Considerations).

Pediatrics:

APO-DIAZEPAM is contraindicated in children under 6 months (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, 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 insufficiency

- Sleep apnea syndrome
- Myasthenia gravis
- Narrow angle glaucoma
- Children under six months of age due to lack of sufficient clinical experience

WARNINGS AND PRECAUTIONS

General

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

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

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression as suicide may occur in such patients. Patients with a history of depression and/or suicide attempts should be kept under close supervision.

Anterograde amnesia may occur with therapeutic doses of benzodiazepines and may be associated with inappropriate behaviour, the risk increasing with higher doses (see ADVERSE REACTIONS).

Concomitant use of alcohol / CNS depressants

The concomitant use of APO-DIAZEPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of APO-DIAZEPAM possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see DRUG INTERACTIONS).

Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

Medical History of Alcohol or Drug Abuse

APO-DIAZEPAM (diazepam) should be used with extreme caution in patients with a history of alcohol or drug abuse.

APO-DIAZEPAM should be avoided in patients with dependence on CNS depressants including alcohol. An exception to the latter is the management of acute withdrawal reactions.

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/Tolerance

Dependence Liability

Use of benzodiazepines and benzodiazepine-like agents may lead to the development of physical and psychic dependence (see ADVERSE REACTIONS).

Tolerance

Some loss of response to the effects of benzodiazepines may develop after repeated use of APO-DIAZEPAM (diazepam) for prolonged time.

Withdrawal

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. Withdrawal symptoms may develop after a lengthy period of use at therapeutic doses. The possibility that such effects may also occur following short-term use, especially at high doses, or if the daily dose is reduced rapidly or abruptly discontinued, should be considered. Symptoms of withdrawal may consist of headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Since these symptoms are similar to those for which the patient is being treated, it may appear that he/she has suffered a relapse upon discontinuation of the drug.

Rebound anxiety is a transient syndrome whereby the symptoms that led to treatment with APO-DIAZEPAM recur in an enhanced form. This may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

Since the risks of withdrawal symptoms and rebound anxiety are greater after abrupt discontinuation of treatment, abrupt withdrawal of the drug should be avoided and treatment – even if only of short duration – should be terminated by gradually reducing the daily dose (see DOSAGE AND ADMINISTRATION, Dosing Considerations.)

Lactose Intolerance

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

Neurologic

Driving and Hazardous Activities

Since diazepam has a central nervous system depressant effect, patients should be warned against driving, operating dangerous machinery, or engaging in other hazardous activities requiring mental alertness and physical coordination. Sedation, amnesia, impaired concentration and impaired muscle function may 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. They also should be warned against the concomitant use of alcohol and other CNS depressant drugs.

Patients receiving APO-DIAZEPAM should be advised to proceed cautiously wherever mental alertness and physical coordination are required.

Psychiatric

Mental and Emotional Disorders

It should be recognized that suicidal tendencies may be present in patients with emotional disorders and that protective measures and appropriate treatment may be necessary and should be instituted without delay.

As with other benzodiazepines, diazepam should not be used in individuals with physiological anxiety or normal stresses of daily living, but only in the presence of disabling manifestations of an appropriate pathological anxiety disorder.

These drugs are not effective in patients with characterological and personality disorders or those with obsessive-compulsive disorders. Diazepam is also not recommended for management of depressive or psychotic disorders. Benzodiazepines should not be used to treat anxiety associated with depression, as suicide may be precipitated in these patients.

Paradoxical reactions:

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

Since excitement and other paradoxical reactions can result from the use of anxiolytic sedatives in psychotic patients, diazepam should not be used in ambulatory patients suspected of having psychotic tendencies.

Respiratory

Respiratory depression may occur following administration of APO-DIAZEPAM. 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 can be avoided by careful adjustment of the dose to individual requirements.

APO-DIAZEPAM should be used with caution in patients with chronic respiratory diseases and a lower dose is recommended due to the risk of respiratory depression.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Special Populations

Pregnant Women:

The safety of diazepam for use in pregnancy has not been established. An increased risk of congenital malformation (e.g., congenital malformations of the heart, cleft lip and/or palate) associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. APO-DIAZEPAM should not be used during pregnancy except if absolutely necessary.

Continuous administration of benzodiazepines during pregnancy may give rise to hypotension, reduced respiratory function and hypothermia in the newborn child. Infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence. Withdrawal symptoms in newborn infants have occasionally been reported with this class of drug. Special care must be taken when APO-DIAZEPAM is used during labour and delivery, as high single doses may produce irregularities in the fetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate. With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants). If the drug is prescribed to a woman of childbearing potential, she should be warned to consult her physician regarding discontinuation of the drug if she plans to become or suspects that she is pregnant.

Nursing Women:

Diazepam passes into breast milk. Breast-feeding is therefore not recommended in patients receiving APO-DIAZEPAM.

Pediatrics:

Not recommended for use in children under six months. See CONTRAINDICATIONS.

Geriatrics:

Elderly and debilitated patients or those with organic brain disorders have been found to be prone to central nervous system depression following even low doses. For these patients it is recommended that the dosage be limited to the smallest, effective amount with incremental increases made gradually depending on the response, to preclude development of ataxia, over sedation or other possible adverse effects (see DOSAGE AND ADMINISTRATION).

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).

Impaired Hepatic or Renal Function

In patients with impaired hepatic or renal function, it is recommended to initiate therapy, if necessary, at a very low dose and to increase the dosage only to the extent that such an increase is compatible with the degree of residual function of these organs. If APO-DIAZEPAM is administered for protracted periods, such patients should be monitored closely and have periodic blood counts and liver function tests.

Use in Epileptic Patients

Careful consideration should be given if APO-DIAZEPAM is to be used in patients with epilepsy as the possibility of an increase in the frequency and/or severity of grand mal seizures may require an increase in the doses of standard anticonvulsant medication. An abrupt withdrawal of APO-DIAZEPAM in such cases may also be associated with the temporary increase in the frequency and/or severity of seizures.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

The most common adverse reactions reported for diazepam are fatigue, drowsiness, muscle weakness and ataxia; they are usually dose-related. These adverse events occur predominantly at the start of therapy and usually disappear with prolonged administration.

Serious and Important Adverse Reactions:

The more serious adverse reactions occasionally reported are leucopenia, jaundice and hypersensitivity.

- Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are recommended during long term therapy.
- Allergic reactions and a very few cases of anaphylaxis have been reported to occur with benzodiazepines.

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.

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

Psychiatric and paradoxical reactions: Release of hostility and other paradoxical effects such as irritability, excitability, restlessness, agitation, aggression, delusion, anger, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur with the use of benzodiazepines. Should this occur, the drug should be discontinued. These effects are more likely to occur in children and in the elderly (see WARNINGS AND PRECAUTIONS - Psychiatric and paradoxical reactions).

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

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 Liability). Abuse of benzodiazepines has been reported (see WARNINGS-General).

Post-Market Adverse Drug Reactions

Other adverse events, listed by body systems, include the following:

Cardiovascular System: Hypotension, circulatory depression, irregular heart rate, cardiac failure including cardiac arrest.

Digestive System: Dry mouth, nausea, gastrointestinal disturbances, constipation and hypersalivation, jaundice.

Metabolic and Nutritional Disorders: increased transaminases, increased blood alkaline phosphatase.

Nervous System: Ataxia, tremor, vertigo, dizziness, headache, slurred speech, dysarthria, confusion, emotional poverty, alertness decreased, depression, libido increased or decreased, euphoria, hypoactivity and memory impairment.

Respiratory System: Respiratory depression including respiratory failure.

Skin and Appendages: Skin rash, generalized exfoliative dermatitis.

Special Senses: Diplopia, vision blurred.

Urogenital System: Incontinence, urinary retention.

Injury, Poisoning and Procedural Complication: 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.

DRUG INTERACTIONS

Drug-Drug Interactions

Pharmacokinetic Drug-Drug Interaction (DDI)

The oxidative metabolism of diazepam, leading to the formation of the active metabolites N-desmethyldiazepam, 3-hydroxydiazepam (temazepam) and oxazepam, is mediated by CYP2C19 and CYP3A cytochrome P450 isoenzymes. As shown by *in vitro* study, the hydroxylation reaction is carried out mainly by CYP3A isoform whereas the N-demethylation is mediated by both CYP3A and CYP2C19. Results from *in vivo* studies in human volunteers have confirmed the *in vitro* observations.

In consequence substrates, which are modulators of CYP3A and or of CYP2C19, may potentially alter the pharmacokinetics of diazepam. Drugs like ritonavir, cimetidine, ketoconazole, itraconazole, clarithromycin, verapamil, erythromycin, diltiazem, fluvoxamine, fluoxetine, and omeprazole which are CYP3A or CYP2C19 inhibitors may lead to increased and prolonged sedation. There have also been reports that the metabolic elimination of phenytoin is affected by diazepam.

Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

Pharmacodynamic Drug-Drug Interaction (DDI)

Enhanced effects on sedation, respiration, and hemodynamics may occur when APO-DIAZEPAM is co-administered with any centrally acting depressants including alcohol, antipsychotics (phenothiazine, thioxanthene and butyrophenone classes), anxiolytics/sedatives, hypnotics, antidepressants (e.g., monoamine oxidase inhibitors, tricyclic antidepressants), anticonvulsants, muscle relaxants, narcotic analgesics, anesthetics and sedative antihistamines. Therefore, if diazepam is to be combined with other drugs acting on the CNS, careful consideration should be given to the pharmacology of the agent involved because of the possible additive or potentiation of drug effects. In the case of narcotic analgesics enhancement of euphoria may also occur, leading to an increase in psychological dependence.

The concomitant use of APO-DIAZEPAM with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of APO-DIAZEPAM possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see WARNINGS AND PRECAUTIONS-Concomitant use of alcohol / CNS depressants). Patients should be advised against the concurrent use of alcohol and other CNS depressant drugs.

Drug-Food Interactions

Interactions with food have not been established. Grapefruit juice decreases the activity of CYP3A4, which is implicated in the metabolism of diazepam, and may contribute to increased plasma levels of the drug.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage for APO-DIAZEPAM (diazepam) should be individualized for maximal beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who may require higher doses.

Lower doses are recommended for elderly and debilitated patients, and patients with debilitating diseases. In the first few days of administration a cumulative effect of drug may occur, and therefore, the dosage should be increased only after stabilization is apparent.

The tablet can be divided into equal halves to facilitate dosing.

The duration of treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment evaluated, especially if the patient is symptom free. It should not exceed 2 - 3 months, including the tapering-off period. Extension beyond this period should not take place without re-evaluation of the situation. It may be useful to inform the patient when treatment is started that it will be of limited duration and explain precisely how the dosage will be progressively decreased. Moreover, it is important that the patient be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms, should they occur during withdrawal. There is evidence that, in the case of short-acting benzodiazepines, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high. When long-acting benzodiazepines such as diazepam are being used, it is important to warn against changing to a short-acting benzodiazepine as withdrawal symptoms may develop.

Recommended Dose and Dosage Adjustment

Children: Because of varied responses, initiate therapy with lowest dose and increase as required. Not for use in children under six months. See CONTRAINDICATIONS. The initial dose should be between 1 mg and 2.5 mg, three or four times daily initially; increase gradually as needed and tolerated.

Adults:

Symptomatic relief of anxiety and tension in psychoneurosis and anxiety reactions: Depending upon severity of symptoms, the initial dose should be between 2 mg and 10 mg, two to four times daily.

Symptomatic relief in acute alcohol withdrawal: The initial dose should be 10 mg, three or four times during the first 24 hours, reducing to 5 mg, three or four times daily as needed.

Adjunctively for relief of skeletal muscle spasm: The initial dose should be between 2 mg and 10 mg, three to four times daily

Elderly and debilitated patients:

The initial dose should be 2 mg, one or two times daily initially, increase gradually as needed and tolerated (see WARNINGS and PRECAUTIONS - Special Populations - Geriatrics, Impaired Hepatic or Renal Function).

OVERDOSAGE

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

Symptoms

The main symptoms of benzodiazepine overdose are drowsiness, over sedation, dysarthria, nystagmus, and ataxia. When the effects of the drug overdose begin to wear off, the patient exhibits some jitteriness and overstimulation. Overdose of diazepam 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.

Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease. There are minimum effects on respiration, pulse and blood pressure unless the overdosage is extreme.

Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

In managing overdosage, consider the possibility of multiple drug involvement.

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory 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.

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

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

Warning: The benzodiazepine receptor antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Diazepam is rapidly and completely absorbed from the gastrointestinal tract, peak plasma concentrations appearing 30 - 90 minutes after oral ingestion.

Distribution: Diazepam and its metabolites are highly bound to plasma proteins (diazepam 98%). The volume of distribution at steady state is 0.8 - 1.0 L/kg. In humans, comparable blood levels of diazepam were obtained in maternal and cord blood indicating placental transfer of the drug.

Metabolism: Diazepam is N-demethylated by CYP3A4 and 2C19 to the active metabolite N-desmethyl diazepam, and is hydroxylated by CYP3A4 to the active metabolite temazepam. N-

desmethyldiazepam and temazepam are both further metabolized to oxazepam. Oxazepam and temazepam are further conjugated to glucuronic acid.

Excretion: The acute half-life is six to eight hours with a slower decline thereafter (half-life up to 48 hours). The terminal elimination half-life of the active metabolite N-desmethyldiazepam is up to 100 hours. Diazepam and its metabolites are excreted mainly in the urine, predominantly in their conjugated forms. The clearance of diazepam is 20 - 30 mL/min.

Special Populations and Conditions

The elimination half-life may be prolonged in the newborn, in the elderly and in patients with liver disease. In renal failure the half-life of diazepam is unchanged.

STORAGE AND STABILITY

Preserve in tight light, resistant containers. Store at room temperature (15°C -30°C).

SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-DIAZEPAM 2 mg: Each white, round, flat-faced, bevelled-edge tablet, scored and engraved "APO" over "2" on one side contains 2 mg of diazepam. Available in bottles of 100 and 1000.

APO-DIAZEPAM 5 mg: Each yellow, round, flat-faced, bevelled-edge tablet, scored and engraved "APO" over "5" on one side contains 5 mg of diazepam. Available in bottles of 100 and 1000.

APO-DIAZEPAM 10 mg: Each blue, round, flat-faced, bevelled-edge tablet, scored and engraved "APO" over "10" on one side contains 10 mg of diazepam. Available in bottles of 100 and 1000.

Non-medicinal ingredients are lactose, microcrystalline cellulose, starch, magnesium stearate, D&C yellow #10 (5 mg only), FD&C yellow #6 (5 mg only), FD&C blue #1 (10 mg only) and FD&C blue #2 (10 mg only).

Composition

In addition to diazepam, each tablet contains the non-medicinal ingredients lactose monohydrate, microcrystalline cellulose, starch, magnesium stearate, D&C yellow #10 (5 mg only), FD&C yellow #6 (5 mg only), FD&C blue #1 (10 mg only) and FD&C blue #2 (10 mg only).

PART II: SCIENTIFIC INFORMATION

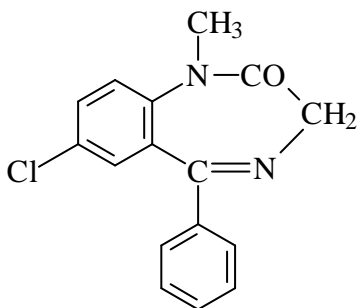
PHARMACEUTICAL INFORMATION

Drug Substance

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

Structural Formula:

Molecular Formula: $C_{16}H_{13}ClN_2O$



Molecular Weight: 284.74

Description: Diazepam is a colorless, crystalline compound, insoluble in water.

DETAILED PHARMACOLOGY

In laboratory animals, diazepam was shown to possess sedative, muscle relaxant and anticonvulsant properties.

Diazepam has a taming effect in fighting mice and vicious monkeys and a calming effect on the irritability of rats with septal lesions. Diazepam causes sedation in cats at a dose which depresses the EEG activity of the cortex, hippocampus, amygdala and septum.

Diazepam is active as a muscle relaxant in the inclined screen test in mice, in blocking decerebrate rigidity in cats and in blocking the spinal reflex in cats anaesthetized with chloralose.

Diazepam has demonstrated anticonvulsant activity in antistrychnine, anti-metrazol, anti-maximal electroshock and, to a lesser degree, anti-minimal electroshock tests in mice.

Diazepam has shown minimal or no effect in anti-Parkinsonism activity in monkeys, anti-emetic activity in dogs, cardiovascular effects in dogs and endocrine effects in rats and rabbits.

TOXICOLOGY

Acute toxicology studies in mice have revealed the following results:

oral LD₅₀ 720 mg/kg

i.v. LD₅₀ >100 mg/kg

In a forty-two week chronic toxicity study in rats diazepam was administered in doses up to and including 240 mg/kg/day; no abnormalities were observed on normal growth, food consumption, blood counts, gross and microscopic findings.

Reproduction studies in rats have been performed with diazepam in oral doses of 1, 10, 80, and 100 mg/kg/day. At the lower dose levels the survival of offspring was within normal limits. Further studies in rats at oral doses up to and including 80 mg/kg/day did not confirm a teratological effect on the offspring. At the 100 mg/kg dose level there was a decrease in the number of pregnancies and surviving offspring and several neonates showed skeletal or other defects.

The carcinogenic potential of oral diazepam has been studied in several rodent species. An increase in the incidence of hepatocellular tumours occurred in male mice. No significant increase in the incidence of tumours was observed in female mice, rats, hamsters or gerbils.

A number of studies have provided weak evidence of a mutagenic potential at high concentrations which are, however, far above therapeutic doses in humans.

Diazepam was found to be teratogenic in mice at dose levels of 45-50 mg/kg, 100 mg/kg, and 140 mg/kg/day as well as in hamsters at 280 mg/kg. In contrast, this drug was shown to be non teratogenic at 80 and 300 mg/kg/day in rats and at 20 and 50 mg/kg/day in rabbits.

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PART III: CONSUMER INFORMATION

 APO-DIAZEPAM

Diazepam Tablets, USP

2 mg, 5 mg, and 10 mg

This leaflet is a part of the "Product Monograph" published for APO-DIAZEPAM 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 APO-DIAZEPAM, read this leaflet before you give the first tablet.

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

ABOUT THIS MEDICATION

What the medication is used for:

- APO-DIAZEPAM is used for the short-term relief of severe anxiety.
- APO-DIAZEPAM is used to reduce muscle spasms caused by medical conditions such as local trauma or by disorders such as cerebral palsy, paraplegia and "stiff man syndrome".
- APO-DIAZEPAM can also be used to treat trembling, confusional states or anxiety associated with alcohol withdrawal

What it does:

APO-DIAZEPAM contains the active ingredient diazepam, which belongs to a group of medicines known as benzodiazepines. APO-DIAZEPAM has sedative properties which help in the treatment of anxiety.

When it should not be used:

- If you are allergic to the group of medicines known as benzodiazepines (examples: clonazepam, chlordiazepoxide, bromazepam, or flurazepam)
- If you are allergic to the medicinal ingredient (diazepam)
- If you are allergic to any other ingredients it contains (see '**What the non-medicinal ingredients are**')
- If you suffer from lung disease or have sleep apnea
- If you have a liver condition
- If you have glaucoma
- If you have myasthenia gravis
- In children under 6 months

What the medicinal ingredient is:

Diazepam

What the nonmedicinal ingredients are:

The non-medicinal ingredients in APO-DIAZEPAM are: lactose monohydrate, microcrystalline cellulose, starch, magnesium stearate, D&C yellow #10 (5 mg only), FD&C yellow #6 (5 mg only), FD&C blue #1 (10 mg only) and FD&C blue #2 (10 mg only)

What dosage forms it comes in:

APO-DIAZEPAM is available as:
2 mg, 5 mg & 10 mg tablets.

WARNINGS AND PRECAUTIONS

- APO-DIAZEPAM may affect your ability to be alert. Driving, operating machinery and other hazardous activities should therefore be avoided altogether or at least during the first few days of treatment. This effect of APO-DIAZEPAM may be made worse if you take alcoholic drinks. If your doctor has increased your dose or if you have changed the timings of when you take your medication this may also modify your reactions.
- You must not consume alcohol or other drugs that affect the central nervous system while taking APO-DIAZEPAM (see INTERACTIONS WITH THIS MEDICATION below).
- Always contact your doctor before stopping or reducing your dosage of APO-DIAZEPAM, as suddenly stopping treatment or a large decrease in dose can cause withdrawal symptoms.
- Benzodiazepines such as APO-DIAZEPAM have produced dependence (addiction) and withdrawal symptoms can occur when treatment is stopped suddenly. The risk of dependence (addiction) increases with higher doses and longer duration of treatment. Symptoms of withdrawal may include shaking, sweating, sleep disturbances, agitation/restlessness, headache, muscle pain, anxiety, 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, and seizures.
- There have been reports of falls and fractures in people who take benzodiazepines such as APO-DIAZEPAM. The risk is increased in those also taking other sedatives (including alcoholic beverages) and in the elderly.
- Memory loss may occur when APO-DIAZEPAM is used at therapeutic doses.
- If you develop any unusual or disturbing thoughts or behaviour while using APO-DIAZEPAM, discuss the matter immediately with your doctor.
 - 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.

- APO-DIAZEPAM passes into breast milk. Therefore, if you are breast feeding, this medicine should be avoided. Your doctor will discuss this with you.

BEFORE you use APO-DIAZEPAM 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 or have a history of dependence /addiction to alcohol or drugs.
- Have a history of depression and/or suicide attempts.
- Have the rare hereditary problems of galactose intolerance.
- Are pregnant or plan on becoming pregnant

INTERACTIONS WITH THIS MEDICATION

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 APO-DIAZEPAM. These medicines include:

- medicines to control seizures
- narcotics and narcotic pain relievers
- muscle relaxants
- sleeping medication
- antihistamines or allergy medications
- medicines to treat your mood, such as monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines
- ritonavir, cimetidine, ketoconazole, clarithromycin
- verapamil, erythromycin, and diltiazem

These medicines may be affected by APO-DIAZEPAM or may affect how well APO-DIAZEPAM 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 APO-DIAZEPAM.

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

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.

	Usual Daily Dose
Adults Relief of Severe anxiety and tension	Depending upon severity of symptoms – 2 mg to 10 mg, two to four times daily.
Relief of Acute Alcohol Withdrawal	10 mg, three or four times during the first 24 hours, reducing to 5 mg, three or four times daily as needed.
Relief of severe muscle spasm	2 mg to 10 mg, three to four times daily.
Elderly	2 mg, one or two times daily initially, increase gradually as needed and tolerated
Children (7 months and older)	1 mg to 2.5 mg, three or four times daily initially; increase gradually as needed and tolerated.

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

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

Your doctor will advise you when to stop taking the medicine. Your doctor will slowly decrease the dosage as sudden discontinuation of treatment can cause the appearance of withdrawal symptoms.

Overdose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications APO-DIAZEPAM 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.

IMPORTANT: PLEASE READ

Consult your doctor or pharmacist as soon as you can if you do not feel well while taking APO-DIAZEPAM.

The most common side effects are:

- Feeling drowsy or tired, especially at the start of treatment.
- Some muscle weakness and dizziness.

Less common possible side effects are:

- Changes in your skin colour, nausea, headache, blurred vision, tremors, hypotension (low blood pressure), urinary incontinence, and constipation.
- Memory loss may occur in some patients using APO-DIAZEPAM.

- In rare cases changes in your blood and liver may occur and your doctor will monitor for these.
- Falls and fractures: The risk is increased in those also taking other sedatives (including alcoholic beverages) and in the elderly.

Withdrawal-related side effects:

- With long-term APO-DIAZEPAM treatment development of physical and psychological dependence may occur. If treatment is stopped suddenly symptoms of withdrawal may occur, including: headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases of withdrawal, symptoms may include numbness and tingling of the extremities, hallucinations, increased sensitivity to light, noise and physical contact, and epileptic seizures.

Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain in the mouth or eyes)			✓ Immediately
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), and thoughts of death or suicide.		✓	

This is not a complete list of side-effects. If you are concerned about these or any other unwanted side-effects, talk to your doctor or pharmacist.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		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		✓	

HOW TO STORE IT

- Keep APO-DIAZEPAM in tight, light resistant containers. Store at room temperature (15°C -30°C).
- Keep this medicine out of the reach and sight of children

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

Fax toll-free to 1-866-678-6789, or

Mail to : Canada Vigilance Program

Health Canada

Address Locator: 0701E

Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:

<http://www.apotex.ca/products>.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: June 5, 2014