PRODUCT MONOGRAPH

APO-DIAZEPAM
Diazepam Tablets, USP

2 mg, 5 mg and 10 mg

Anxiolytics: Benzodiazepine derivatives

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

DATE OF REVISION:
September 19, 2018

Control #: 219491

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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 WARNINGS AND PRECAUTIONS, Special Populations, 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 impairment (see WARNINGS AND PRECAUTIONS, Hepatic).
- Sleep apnea syndrome.
- Myasthenia gravis.
- Narrow angle glaucoma.

- Children under six months of age due to lack of sufficient clinical experience.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions:
RISKS FROM CONCOMITANT USE WITH OPIOIDS

Concomitant use of APO-DIAZEPAM and opioids may result in profound sedation, respiratory depression, coma and death (see **WARNINGS AND PRECAUTIONS**, **General**, **Concomitant use with opioids**).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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 with opioids
Concomitant use of benzodiazepines, including APO-DIAZEPAM, 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 inadequate.

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 opioid analgesics.

If a decision is made to prescribe APO-DIAZEPAM 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 APO-DIAZEPAM than indicated in the absence of an opioid and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking diazepam, 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 DRUG INTERACTIONS and OVERDOSE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when APO-DIAZEPAM 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.

Concomitant use of alcohol and/or centrally acting 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, that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see DRUG INTERACTIONS and OVERDOSE).

Patients should be advised against the concurrent use of APO-DIAZEPAM with alcohol and/or 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).

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.

Dependence/Tolerance
Dependence Liability
Use of APO-DIAZEPAM may lead to the development of physical and psychological dependence (see ADVERSE REACTIONS). Benzodiazepines are commonly abused in conjunction with other drugs (see DRUG INTERACTIONS).

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 with APO-DIAZEPAM 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, diarrhea, muscle pain, extreme anxiety, tension, restlessness, confusional state 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 convulsions. 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, sleep disturbances, 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.)
Withdrawal symptoms may also develop when switching from APO-DIAZEPAM to a benzodiazepine with a considerably shorter elimination half-life.

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.

Hepatic
APO-DIAZEPAM is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS). APO-DIAZEPAM, like other benzodiazepines can precipitate or exacerbate hepatic encephalopathy.

Special caution should be exercised when administering APO-DIAZEPAM to patients with mild to moderate hepatic impairment. In patients with cirrhosis, a 2-to 5-fold increase in mean half-life has been reported. Increases in half-life have also been reported in hepatic fibrosis and in both chronic and acute hepatitis. The reduced clearance of diazepam and its active metabolite (desmethyl-diazepam) leads to their increased accumulation during long-term dosing. This in turn is associated with increased sedation (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). If treatment is necessary in patients with impaired hepatic function, it is recommended to initiate APO-DIAZEPAM 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 hepatic function. If APO-DIAZEPAM is administered for protracted periods, such patients should be monitored closely and have periodic liver function tests.

Neurologic
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.

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 APO-DIAZEPAM with alcohol and/or 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, anxiety, delusion, anger, 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.

Renal

If treatment is necessary in patients with impaired renal function, it is recommended to initiate APO-DIAZEPAM 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 renal function. If APO-DIAZEPAM is administered for protracted periods, such patients should be monitored closely.

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.

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 APO-DIAZEPAM is prescribed to a woman of childbearing potential, she should be warned to consult her physician regarding discontinuation of APO-DIAZEPAM 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 of APO-DIAZEPAM 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).

Monitoring and Laboratory Tests
If APO-DIAZEPAM is administered for protracted periods, patients with impaired hepatic or renal function should be monitored closely. Because of isolated reports of neutropenia and jaundice, periodic blood counts and liver function tests are recommended during long term therapy.

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 and mood disturbances, decreased alertness, depression, changes in libido, 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

Serious Drug Interactions:
Concomitant use of APO-DIAZEPAM and opioids (see WARNINGS AND PRECAUTIONS - Serious Warnings and Precautions, General – Concomitant Use with opioids; Pharmacodynamic Drug-Drug Interactions)

Overview

The concomitant use of APO-DIAZEPAM with opioids, alcohol and/or other CNS depressants should be avoided as this increases the risk of profound sedation, respiratory depression, coma and death.

If APO-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 pharmacodynamic drug effects.

Avoid concomitant us of sodium oxybate with APO-DIAZEPAM as this may lead to increased risk of respiratory depression

APO-DIAZEPAM is not recommended for concomitant use with clozapine and/or for concomitant parenteral use with olanzapine.

The metabolism of diazepam and its main metabolite, desmethyldiazepam depends on the cytochrome P450 isozymes CYP3A4 and CYP2C19. Modulators of these enzymes may lead to changes in diazepam disposition and effects. Stronger interactions are seen with compounds that affect more than one of diazepam's oxidative metabolic pathways. Inhibitors of CYP3A4 and/or CYP2C19 decrease metabolic rate and may lead to higher than normal concentrations of diazepam and the desmethyl metabolite and consequently to increased or prolonged sedation and anxiolytic effects. Such changes may exacerbate diazepam's effects in patients with increased sensitivity, e.g. due to their age, reduced liver function or treatment with other drugs that impair oxidation. Inducers of CYP3A4 and CYP2C19 may lead to lower than expected concentrations and hence to a lack of desired efficacy.

Monitoring of serum level of phenytoin is recommended when initiating or discontinuing APO-DIAZEPAM.

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. This may result in excessive or prolonged sedation. Patients should be advised to avoid grapefruit juice while taking APO-DIAZEPAM.

Drug-Drug Interactions

Pharmacokinetic Drug-Drug Interaction (DDI)

Effect of other drugs on the pharmacokinetics of diazepam

Enzyme inhibitors

Antimycotic azole derivatives (ketoconazole, itraconazole, fluconazole and voriconazole) inhibit CYP3A4 and CYP2C19 pathways and lead to increased exposure to diazepam. In a clinical trial using a single dose

of 5 mg diazepam, fluconazole increased the AUC of diazepam 2.5-fold and prolonged elimination half-life from 31 h to 73 h, while voriconazole increased the AUC of diazepam 2.2-fold and prolonged elimination half-life from 31 h to 61 h. This may result in increased and prolonged sedation. Therefore, it is recommended to avoid concomitant use of these drugs with APO-DIAZEPAM or reduce the dose of APO-DIAZEPAM.

Serotonin reuptake inhibitors (fluvoxamine and fluoxetine): Fluvoxamine inhibits CYP3A4 and CYP2C19 degradation pathways. In a clinical trial using a single dose of 10 mg diazepam, fluvoxamine increased the AUC of diazepam 3-fold and prolonged elimination half-life from 51 h to 118 h. Exposure and time to reach steady state of the desmethyl metabolite was also increased. Fluoxetine is a moderate inhibitor of CYP3A4. Fluvoxamine and fluoxetine may lead to increased and prolonged sedation. For patients taking fluvoxamine, a benzodiazepine metabolized via a non-oxidative pathway is recommended. Patients administering fluoxetine with APO-DIAZEPAM should be monitored closely.

Combined hormonal contraceptives appear to reduce the clearance and prolong elimination half- life of diazepam. Monitor clinical response of APO-DIAZEPAM in women taking concomitant oral contraception. There is some evidence that benzodiazepines can increase the incidence of break- through bleeding in women with hormonal contraceptives.

The proton pump inhibitors omeprazole and esomeprazole are CYP2C19 and CYP3A4 inhibitors. When administered at a dose of 20 mg o.d., omeprazole increased the diazepam AUC by 40% and the half-life by 36%; at a dose of 40 mg o.d., omeprazole increased the diazepam AUC by 122% and the half-life by 130%. The elimination of desmethyl-diazepam was reduced as well. The effect of omeprazole was seen in extensive but not slow metabolizers of CYP2C19. When administered at a dose of 30 mg o.d., esomeprazole increased the AUC and half-life of diazepam by 80%. Therefore, it is recommended to monitor patients administering these drugs with diazepam and reduce the dose of APO-DIAZEPAM if necessary.

The histamine H_2-receptor antagonist cimetidine, an inhibitor of multiple CYP isozymes, including CYP3A4 and CYP2C19, reduces the clearance of diazepam and of desmethyl- diazepam by 40 to 50%. This results in higher exposure to and a prolonged elimination half-life of diazepam and its main metabolite after single dosing and to higher steady-state concentrations after multiple dosing of diazepam. Enhanced sedation was also seen with co-administration of cimetidine. Therefore, when used with cimetidine, a reduction of the dose of APO-DIAZEPAM may be necessary.

Disulfiram inhibits the metabolism of diazepam and probably the further metabolism of diazepam's active metabolites. Enhanced sedative effects may result.

Antituberculosis agent therapy may change the disposition of diazepam. In presence of isoniazid diazepam mean exposure (AUC) and half-life were increased (on average 33 to 35%) with the largest changes seen in subjects with slow-acetylator phenotype. When used with isoniazid, monitor patients and reduce the dose of APO-DIAZEPAM if necessary.

The calcium channel blocker diltiazem, a substrate for the same CYP isozymes as diazepam and an inhibitor of CYP3A4, increased AUC by approximately 25% and prolonged half-life by 34 to 43% of diazepam in poor and extensive CYP2C19 metabolizers. In the presence of diltiazem, exposure to desmethyl-diazepam also tended to increase. Exercise caution when using APO-DIAZEPAM with diltiazem, irrespective of CYP2C19 metabolizer status.

Idelalisib is a strong CYP3A4 inhibitor that increases the serum concentrations of diazepam. When used with idelalisib, monitor patients and reduce the dose of APO-DIAZEPAM if necessary.

The psychostimulant modafinil induces CYP3A4 and inhibits CYP2C19. This may prolong the elimination of diazepam and cause excessive sedation. When used with modafinil, monitor patients and reduce the dose of APO-DIAZEPAM if necessary.

Other CYP3A or CYP2C19 inhibitors, such as clarithromycin, erythromycin, ritonavir and verapamil, may lead to increased and prolonged sedation of APO-DIAZEPAM.

Enzyme inducers

Rifampicin potently induces CYP3A4 and has also a significant accelerating effect on the CYP2C19 pathway. When dosed at 600 mg or 1200 mg daily for 7 days, diazepam clearance was increased approximately 4-fold and AUC decreased by approximately 75%. A significant reduction in exposure to all diazepam metabolites was also observed. APO-DIAZEPAM should not be used in combination with rifampicin.

Carbamazepine is a known inducer of CYP3A4 and accelerated elimination (increased clearance, reduced half-life) of diazepam 3-fold while increasing concentrations of desmethyl-diazepam.
This can result in a reduced effect of APO-DIAZEPAM.

Other pharmacokinetic interactions

Diazepam pretreatment changes the pharmacodynamics and pharmacokinetics of the anaesthetic ketamine. Ketamine N-demethylation was inhibited leading to a prolonged half-life and prolonged ketamine-induced sleeping time. In the presence of APO-DIAZEPAM, a reduced ketamine concentration is required to achieve adequate anaesthesia.

Antacids may lower the rate but will not lower the extent of diazepam absorption from the tablet; this may lead to attenuated effects after a single dose but not influence steady-state concentrations during multiple-dose therapy.

Prokinetic drugs increase the rate of diazepam absorption, potentially resulting in a transient increase in sedation. Intravenous but not oral metoclopramide increases the rate of absorption of diazepam and increases the maximum concentration achieved after oral dosing.

Effect of diazepam on the pharmacokinetics of other drugs

Phenytoin therapy was associated with higher concentrations and increased phenytoin intoxication when combined with diazepam in some, but not all, studies. Monitoring of serum level of phenytoin is recommended when initiating or discontinuing APO-DIAZEPAM.

Pharmacodynamic Drug-Drug Interaction

Concomitant use with opioids, alcohol and/or other central nervous system (CNS) depressants

Due to additive CNS depressant effect, the concomitant use of APO-DIAZEPAM with opioids, alcohol and/or other CNS depressants (anxiolytic/sedatives, anesthetics, hypnotics and sedative antihistamines) should be avoided. Concomitant use of APO-DIAZEPAM with these increases the risk of profound sedation, respiratory depression, coma and death. Patients should be advised against concurrent use. Concomitant prescribing of APO-DIAZEPAM and opioids should be reserved for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of APO-

DIAZEPAM and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see WARNINGS & PRECAUTIONS - Serious Warning and Precautions box, General - Concomitant with opioids, Concomitant use with alcohol and/or CNS depressants).

When combined with narcotic agents, APO-DIAZEPAM may enhance euphoria, leading to an increased risk of abuse or dependence. Diazepam increased the subjective and sedative opioid effects of methadone and buprenorphine in a manner that may heighten abuse potential. A significantly greater deterioration in reaction time was also observed when these drugs were combined with diazepam.

Additive/Potentiated effects with other centrally-acting agents

If APO-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. Additive CNS depressant effects resulting in enhanced sedation and cardio respiratory depression may occur when APO-DIAZEPAM is co-administered with anticonvulsants; muscle relaxants, monoamine oxidase inhibitor and tricyclic antidepressants;; and phenothiazine, thioxanthene and butyrophenone antipsychotics. Sedation, respiratory depression and airway obstruction was reported with the combined use of methotrimeprazine and diazepam.

Avoid concomitant use of sodium oxybate with APO-DIAZEPAM as this may lead to increased risk of respiratory depression.

There are several reports of excessive sedation, loss of consciousness, severe hypotension, or cardiorespiratory depression sometimes resulting in death in patients under combined treatment with clozapine or olanzapine and benzodiazepines, including APO-DIAZEPAM. Concomitant use of APO-DIAZEPAM and clozapine or parenteral use of APO-DIAZEPAM and olanzapine are not recommended.

Antagonistic interactions with centrally acting agents

Reversible loss of control of Parkinson's disease has been seen in some patients treated with combined levodopa and APO-DIAZEPAM.

The xanthines theophylline and caffeine oppose the sedative and possibly anxiolytic effects of APO-DIAZEPAM partially through blocking of adenosine receptors.

Drug-Food Interactions

Grapefruit juice contains strong inhibitors of CYP3A4. Diazepam exposure was strongly increased (AUC 3.2-fold; C_{max} 1.5-fold) and time to reach maximum concentration was delayed when diazepam was given with grapefruit juice instead of water. This may result in excessive or prolonged sedation. Patients should be advised to avoid grapefruit juice while taking APO-DIAZEPAM.

Concurrent consumption of caffeine-containing foods and beverages may result in reduced sedative and anxiolytic effects of APO-DIAZEPAM.

Food may lower the rate but will not lower the extent of diazepam absorption from the tablet; this may lead to attenuated effects after a single dose but not influence steady-state concentrations during multiple-dose therapy.

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).

Driving, operating machinery and other hazardous activities should be avoided while taking APO-DIAZEPAM. Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery.

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 to 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: Benzodiazepine pharmacologic effects appear to be greater in elderly patients than in younger patients even at similar plasma benzodiazepine concentrations, possibly because of age-related changes in drug–receptor interactions, post-receptor mechanisms and organ function. Therefore,

the initial dose of APO-DIAZEPAM should be 2 mg, one or two times daily initially, increase gradually as needed and tolerated (see WARNINGS and PRECAUTIONS - Special Populations - Geriatrics).

Hepatic impairment: APO-DIAZEPAM is contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS; WARNINGS and PRECAUTIONS - Hepatic). Special caution should be exercised when administering APO-DIAZEPAM to patients with mild to moderate hepatic impairment. If treatment is necessary, it is recommended to initiate APO-DIAZEPAM 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 hepatic function. If APO-DIAZEPAM is administered for protracted periods, such patients should be monitored closely and have periodic liver function tests.

Renal impairment: If treatment is necessary in patients with impaired renal function, it is recommended to initiate APO-DIAZEPAM 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 renal function. If APO-DIAZEPAM is administered for protracted periods, such patients should be monitored closely.

OVERDOSAGE

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

Symptoms

The main symptoms of benzodiazepine overdosage are drowsiness, over sedation, dysarthria, nystagmus, and ataxia. When the effects of the drug overdosage 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 to 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., resedation) have subsided.

- Particular caution is necessary when using flumazenil in cases of multiple drug overdosage, since the toxic effects (cardiac arrhythmias and/or convulsions) of other psychotropic drugs, especially cyclic antidepressants, may increase as the effects of benzodiazepines subside. Flumazenil is contraindicated in patients who are showing signs of serious cyclic antidepressant overdose.

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

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

ACTION AND CLINICAL PHARMACOLOGY

Pharmacokinetics

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

Following daily dosing, diazepam levels reach a steady state within approximately 5 days; it takes about twice as long before desmethyl-diazepam levels reach a steady-state. Average steady-state levels of diazepam after once daily administration are approximately twice as high as the peak levels of the drug after the first dose.
During treatment, the elimination half-life of diazepam may increase by 50% due to a reduction in hepatic clearance.

Distribution:
Diazepam is widely distributed into tissues despite high binding to plasma proteins (98 to 99%), mainly albumin and to lesser extent α1-acid glycoprotein. After intravenous administration, a pronounced distribution phase is seen in plasma concentrations with a half-life of distribution of up to 3 hours. The volume of distribution at steady state averages between 0.88 to 1.1 L/kg when derived from plasma concentration measurements. Both protein binding and volume of distribution of desmethyl-diazepam are similar to those of diazepam.

Cerebrospinal fluid (CSF) levels in man following single and multiple doses approximate closely the free drug concentration in plasma. Upon multiple dosing desmethyl-diazepam, but not diazepam, may significantly accumulate in CSF. Diazepam has very rapid uptake into and equilibration with brain tissue, with equilibrium concentrations in brain exceeding those in plasma.

In humans, comparable blood levels of APO-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-desmethyldiazepam, a pathway accounting for 50 to 60% of total diazepam clearance; 3- hydroxylation (27% of total diazepam clearance) is slow, leading to only low plasma levels of the oxidation products temazepam and oxazepam. Oxazepam and temazepam are further conjugated to glucuronic acid.

Oxidation of diazepam is mediated by cytochrome P450 isozymes; formation of desmethyl- diazepam mainly by CYP2C19 and CYP3A and 3-hydroxy-diazepam (temazepam) and oxazepam by CYP3A.

Because CYP2C19 is polymorphic, extensive metabolizers (EMs), and poor metabolizers (PMs) of diazepam can be distinguished. PMs of diazepam showed significantly lower clearance (12 vs 26 mL/min) and longer elimination half-life (88 vs 41 h) of diazepam than EMs after a single oral dose. Also, PMs had lower clearance, higher AUC and longer elimination half-life of desmethyl-diazepam.

Excretion: The acute half-life is six to eight hours with a slower decline thereafter. Typical terminal elimination half-life values are in the range of 24 to 48 hours for diazepam and 40 to 100 hours for the active metabolite desmethyldiazepam. The clearance of diazepam is 20 to 40 mL/min.

Diazepam is almost completely metabolized before leaving the body. Oxazepam-glucuronide is the main drug-related product in urine.

Special Populations and Conditions

Geriatric Population
The unbound fraction of diazepam correlates positively with age and was higher in elderly than in young subjects. Age decreases the capacity of the liver for N-demethylation and 3- hydroxylation of diazepam. An age-dependent decrease in clearance of unbound drug occurs and is responsible for the observed 2 to 4 fold increase in elimination half-life in the elderly, with a stronger effect seen in males than females. Hence the extent of accumulation of unbound pharmacologically active diazepam in elderly persons during multiple dosing will be greater than in younger adults.

Hepatic impairment
Disposition of both diazepam and desmethyl-diazepam is altered in liver disease. In acute viral hepatitis, the half-life of diazepam is increased by about 2-fold but returns slowly to normal on recovery. A more marked (2- to 5-fold) increase in the elimination half-life is seen in patients with alcoholic cirrhosis. These changes are primarily due to impaired hepatic metabolism; altered distribution due to changes in protein binding may be contributory. The reduced clearance of diazepam and desmethyl-diazepam leads to their increased accumulation during long-term dosing. This in turn is associated with increased sedation.

Renal impairment
In chronic renal failure, elimination of diazepam, as indicated by clearance of unbound drug, was similar to that in healthy volunteers. Due to changes in plasma protein binding and tissue distribution of diazepam its elimination half-life was shortened in renal disease from (mean ±S.E.) 92 ±23 h in control to 37 ±7 h in renal failure subjects.

Pregnancy
Diazepam and desmethyl-diazepam readily cross the placental barrier. The fetus can also carry out N-demethylation of diazepam. Long-term treatment leads to accumulation of both compounds in the fetus with high levels in the fetal heart, lungs and brain.

Plasma protein binding of diazepam is decreased during pregnancy, particularly during the last trimester, partly due to the fall in serum albumin concentration. Increased pharmacological effects may result after acute dosing. (see WARNINGS AND PRECAUTIONS, Special Population, Pregnant Women)

Breast-feeding mothers
Diazepam and its metabolites are excreted in breast milk. Normalized for body weight, approximately 5% of the mother's dose reaches the baby. These amounts transferred may be large enough to show effects in the baby. (see WARNINGS AND PRECAUTIONS, Special Population, Nursing Women).

STORAGE AND STABILITY
Preserve in tight light, resistant containers. Store at room temperature (15°C to 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.

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

PART II: SCIENTIFIC INFORMATION

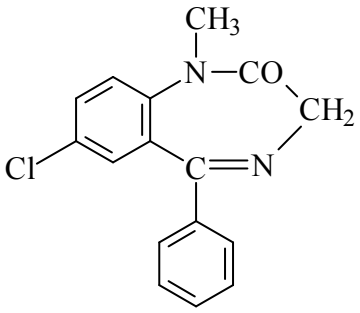
PHARMACEUTICAL INFORMATION

Drug Substance

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

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

Structural Formula:



Molecular Weight: 284.74 g/mol

Physicochemical Properties: Diazepam is a benzodiazepine derivative. 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:

1) oral LD_{50}	720 mg/kg
2) i.v. LD_{50}	>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 to 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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3. Goldberg HL, Finnerty RJ. The comparative efficacy of buspirone and diazepam in the treatment of anxiety. American Journal of Psychiatry 1979;136: 1184-1187.
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5. Lorish TR, Thorsteinsson G, Howard FM. Stiff-man syndrome updated. Mayo Clinic Proceedings 1989;64:629-636.
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8. Product Monograph - VALIUM® 5 mg Tablets. Hoffmann-La Roche Ltd. Date of Revision April 17, 2018 (Control Number 212691)

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

What dosage forms it comes in:
APO-DIAZEPAM is available as:
2 mg, 5 mg & 10 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Taking APO-DIAZEPAM with opioid medicines can cause severe drowsiness, decreased awareness, breathing problems, coma and death.

- 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 or switched to another benzodiazepine. 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 interact with APO-DIAZEPAM. These medicines include:
- medicines to control seizures (flumazenil, carbamazepine, phenytoin)
- narcotics and narcotic pain relievers (opioids) (see **Serious Warnings and Precautions** box)
- muscle relaxants
- sleeping medication or hypnotics (ketamine)
- antihistamines or allergy medications.
- medications to control fungus infections (ketoconazole, itraconazole, fluconazole and voriconazole)
- medications to control viral infections (ritonavir)
- birth control medications
- medications to help digestion, prevent heartburn (such as antacids omeprazole or esomeprazole) or treat ulcers (cimetidine)
- medications to treat cancer of the blood (idelalisib)
- medications to treat addiction to drugs (methadone, buprenorphine) or alcohol (disulfiram)
- antibiotic medications to treat bacterial infections, including tuberculosis (clarithromycin, erythromycin, isoniazid, rifampicin)
- medications used to treat high blood pressure (diltiazem, verapamil)
- medications used to treat narcolepsy and shift work disorder (modafinil, sodium oxybate)
- medicines to treat your anxiety or mood, such as monoamine oxidase inhibitors, tricyclic antidepressants, serotonin specific reuptake inhibitors (fluvoxamine, fluoxetine)
- medications to treat psychosis (methotrimeprazine, clozapine, olanzapine)
- medications to treat Parkinson's disease (levodopa)
- medications to help you stay awake (theophylline and caffeine)

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.

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

Do not drink grapefruit juice during the time that you are taking APO-DIAZEPAM.

If you have not told your doctor about any of the above, tell him/her before you start taking 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. 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.

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 medical help
		Only if severe	In all cases	
Rare	Unusual behavioural problems (aggression, rage, sudden anxiety or excitation; restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behaviour		✓	
	Allergic reactions			✓

	(red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters of the skin, sores or pain 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.

HOW TO STORE IT

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/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.

MORE INFORMATION

If you want more information about APO-DIAZEPAM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

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

Last revised: September 19, 2018