PRODUCT MONOGRAPH

APO-BROMAZEPAM

Bromazepam Tablets

Tablets, 1.5 mg, 3 mg and 6 mg

Apotex Standard

Anxiolytic - Sedative

APOTEX INC.
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1.5 mg, 3 mg and 6 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Tablets, 1.5 mg, 3 mg and 6 mg	**Tablets 1.5 mg:** lactose monohydrate, magnesium stearate, microcrystalline cellulose, starch **Tablets 3 mg:** D&C Red #30 Aluminum Lake 30%, D&C Red #7 Toner Calcium Lake 50%, lactose monohydrate, magnesium stearate, microcrystalline cellulose (PH102), starch **Tablets 6mg:** Brilliant Blue FCF AL Lake 12%, D&C Yellow #10 Aluminum Lake 16%, ferric-ferrous oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose (PH102), starch

INDICATIONS AND CLINICAL USE

APO-BROMAZEPAM (bromazepam) is useful for the short-term, symptomatic relief of manifestations of excessive anxiety in patients with anxiety neurosis.

Geriatrics:
Long-term use of APO-BROMAZEPAM should be avoided in elderly patients. Enhanced monitoring is recommended (see **WARNINGS AND PRECAUTIONS, Falls and fractures; DOSAGE AND ADMINISTRATION, Dosing considerations**).

Pediatrics:
APO-BROMAZEPAM is not recommended for children under 18 years of age (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

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.
- Myasthenia gravis
- Severe hepatic impairment (see **WARNINGS AND PRECAUTIONS, Impaired Hepatic Function**)
- Severe respiratory insufficiency
- Sleep apnea syndrome
- Narrow angle glaucoma

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including APO-BROMAZEPAM, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing APO-BROMAZEPAM
- Monitor all patients regularly for the development of these behaviours or conditions.
- APO-BROMAZEPAM should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like APO-BROMAZEPAM, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of APO-BROMAZEPAM.
- Terminate treatment with APO-BROMAZEPAM by gradually tapering the dosage schedule under close monitoring. (see **WARNINGS AND PRECAUTIONS, Dependence/Tolerance**)

Risks from Concomitant use with Opioids

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

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.

- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

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

APO-BROMAZEPAM (bromazepam) is not recommended for use in patients with depressive disorders or psychosis.

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

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

- **Concomitant use with opioids:** Concomitant use of benzodiazepines, including APO-BROMAZEPAM, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; DRUG INTERACTIONS, Serious Drug Interactions**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe APO-BROMAZEPAM 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-BROMAZEPAM than indicated and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking APO-BROMAZEPAM, 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 **OVERDOSE**).

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

Dependence/Tolerance

Use of benzodiazepines, such as APO-BROMAZEPAM, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short- term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with APO-BROMAZEPAM with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing APO-BROMAZEPAM. In individuals prone to substance use disorder, APO-BROMAZEPAM should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- APO-BROMAZEPAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving opioids should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal

Benzodiazepines, such as APO-BROMAZEPAM, can produce withdrawal symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behavior.

Other withdrawal symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and

physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

(see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; DOSAGE AND ADMINISTRATION, Dosing Considerations**)

Rebound anxiety

Rebound anxiety, a transient syndrome whereby the symptoms that led to treatment with APO-BROMAZEPAM recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, sleep disturbances and restlessness. Since the risk of withdrawal symptoms and rebound anxiety is greater after abrupt discontinuation of treatment, abrupt withdrawal of the APO-BROMAZEPAM should be avoided and treatment - even if only of short duration - should be terminated by gradually reducing the daily dose.

Falls and fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Lactose Intolerance

Lactose monohydrate is a non-medicinal ingredient in APO-BROMAZEPAM. 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 bromazepam 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 and impaired muscular function may adversely affect the ability to drive or operate machinery. This effect is increased if the patient has had alcohol (see **DRUG INTERACTIONS**).

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.

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.

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

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

As with other benzodiazepines, APO-BROMAZEPAM 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. APO-BROMAZEPAM 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.

Respiratory

Respiratory depression may occur following administration of APO-BROMAZEPAM. This effect may be aggravated by pre-existing airway obstruction or brain damage or if other medications which depress respiration have been given. As a rule, this effect can be avoided by careful adjustment of the dose to individual requirements.

APO-BROMAZEPAM should be used with caution in patients with chronic respiratory diseases (see CONTRAINDICATIONS).

Special Populations

Pregnant Women: The safety of use of bromazepam in pregnancy has not been established. Therefore, APO-BROMAZEPAM should not be used during pregnancy. Several studies have suggested an increased risk of congenital malformations (e.g., congenital malformations of the heart, cleft lip and/or palate) associated with the use of the benzodiazepines chlordiazepoxide and

diazepam, and meprobamate, during the first trimester of pregnancies. Since APO-BROMAZEPAM is also a benzodiazepine derivative, its administration is rarely justified in women of childbearing potential. Administration of APO-BROMAZEPAM during the last three months of pregnancy or during labour is allowed only in the event of a strict medical indication, when the expected benefits to the patient outweigh the possible risks to the fetus. Due to the pharmacological action of the product, effects such as irregular heartbeat in the unborn child, hypothermia, hypotonia, moderate respiratory depression, and poor feeding in the neonate can be expected. Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. If APO-BROMAZEPAM is prescribed to a woman of child-bearing potential, she should be warned to consult her physician regarding discontinuation of APO-BROMAZEPAM if she plans to become or suspects that she is pregnant.

Nursing Women: Bromazepam and its metabolites are probably excreted in human milk. Therefore, this drug should not be given to nursing mothers.

Pediatrics: Because of the lack of sufficient clinical experience, APO-BROMAZEPAM is not recommended for use in patients less than 18 years of age.

Geriatrics: Long-term use of APO-BROMAZEPAM should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

Impaired Hepatic Function
Benzodiazepines may have a contributory role in precipitating episodes of hepatic encephalopathy in patients with severe hepatic impairment. These patients should not be treated with APO-BROMAZEPAM (see **CONTRAINDICATIONS**). Special caution should be exercised when administering APO-BROMAZEPAM to patients with mild to moderate hepatic impairment.

In patients with mild to moderate hepatic impairment, it is recommended to initiate APO-BROMAZEPAM, 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 hepatic function. Such patients should be followed closely and have periodic laboratory assessments.

Impaired Renal Function
In patients with impaired renal function, it is recommended to initiate APO-BROMAZEPAM, 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 renal functions. Such patients should be followed closely and have periodic laboratory assessments**.**

Monitoring and Laboratory Tests
If repeated cycles of APO-BROMAZEPAM should be administered, periodic blood counts and liver function tests are advisable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Most Frequent Adverse Reactions:

The most frequently reported adverse reactions with APO-BROMAZEPAM are related to CNS effects and include drowsiness, ataxia and dizziness. These phenomena occur predominantly when starting APO-BROMAZEPAM and usually disappear with repeated administration.

Serious and Important Adverse Reactions:

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

Allergic reactions and a very few cases of anaphylaxis have been reported to occur with benzodiazepines.

Release of hostility and other paradoxical reactions such as irritability, excitability, restlessness, agitation, aggressiveness, delusion, anger, nightmares, hallucinations, psychosis, inappropriate behaviour and other adverse behavioural effects are known to occur with the use of benzodiazepines. They are more likely to occur in children and elderly patients than in other patients. If these occur, use of APO-BROMAZEPAM should be discontinued.

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

Chronic use (even at therapeutic doses) may lead to the development of physical and psychological drug dependence: discontinuation of APO-BROMAZEPAM may result in withdrawal or rebound phenomena (see **WARNINGS AND PRECAUTIONS**).

Abuse of benzodiazepines is more common in poly-drug abusers.

Post-Market Adverse Drug Reactions

Other side effects which can occur, listed by body systems, include the following:

Cardiovascular System: Cardiac failure including cardiac arrest; hypotension, palpitations, tachycardia.

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

Digestive System: Dry mouth, nausea, non-specific gastrointestinal disturbances, vomiting.

Hemic and Lymphatic System: Decreased hemoglobin and hematocrit, increased and decreased WBC.

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Metabolic and Nutritional Disorders: Increased and decreased blood sugar levels, elevations of alkaline phosphatase, bilirubin, SGOT, SGPT.

Musculoskeletal System: Muscle weakness, muscle spasm.

Nervous System: Drowsiness, headache, dizziness, decreased alertness, ataxia, fatigue, seizures, confusional state, disorientation, emotional and mood disturbances, nervousness, anxiety, abnormal dreams, hyperactivity, depression, euphoria, changes in libido.

Respiratory Disorders: Respiratory depression.

Skin and Subcutaneous Tissue Disorders Appendages: Pruritus, rash.

Special Senses: Diplopia, blurred vision.

Urogenital System: Incontinence.

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of APO-BROMAZEPAM and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see **WARNINGS AND PRECAUTIONS BOX, General, Risks from Concomitant use with Opioids)**

Drug-Drug Interactions

Pharmacokinetic Drug-Drug Interaction (DDI)

The specific enzymes involved in the metabolism of bromazepam have not been fully elucidated. There is a possibility that compounds which inhibit key oxidative hepatic enzymes may enhance the activity of benzodiazepines. Co-administration of cimetidine, a multi-CYP inhibitor, and possibly propranolol may prolong the elimination half-life of bromazepam through a substantially reduced clearance (with cimetidine reduction by 50%). Combined administration

with fluvoxamine, an inhibitor of CYP1A2, results in significantly increased bromazepam exposure (2.4-time increase in AUC) and elimination half-life (1.9-time).

Bromazepam at therapeutic doses does not change the pharmacokinetics of co-administered antipyrine, a substrate of several CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C18, and CYP3A4). Furthermore, bromazepam did not induce major CYP450 isozymes in vitro at the level of mRNA; also it did not activate nuclear hormone receptors. Therefore, bromazepam is unlikely to cause pharmacokinetic drug-drug interactions based on CYP450 induction.

Pharmacodynamic Drug-Drug Interaction (DDI)

CNS-acting drugs

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when APO-BROMAZEPAM is co-administered with any centrally acting depressants including alcohol, narcotics, narcotic analgesics, barbiturates, non-barbiturate hypnotics, antihistamines, phenothiazines, thioxanthenes, butyrophenones classes of antipsychotics, anxiolytics/ sedatives, anesthetics, monoamine oxidase inhibitors, tricyclic antidepressants and anticonvulsants (see **WARNINGS AND PRECAUTIONS, Concomitant use of alcohol / CNS depressants, and OVERDOSAGE** sections).

Because of the enhancement of side effects that might occur, patients should be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol during the administration of APO-BROMAZEPAM.

Opioids

Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including APO-BROMAZEPAM, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Enhancement of euphoria may also occur, leading to an increase in dependence. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see **Serious Warning and Precautions box**, and **WARNINGS AND PRECAUTIONS, Concomitant use with opioids** sections).

Drug-Lifestyle Interactions

The concomitant use of APO-BROMAZEPAM with alcohol should be avoided. Such concomitant use has the potential to increase the clinical effects of APO-BROMAZEPAM 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

- APO-BROMAZEPAM should always be prescribed at the lowest effective dose for the shortest duration possible.
- APO-BROMAZEPAM can produce withdrawal symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see **SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; WARNINGS AND PRECAUTIONS, Dependence/Tolerance)**. Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see **WARNINGS AND PRECAUTIONS, Falls and Fractures)**.
- Long-term use of APO-BROMAZEPAM should be avoided in elderly patients. Enhanced monitoring is recommended.

Patients should be evaluated carefully at the start of treatment in order to minimize the dosage and/or the frequency of administration and to prevent overdose due to accumulation.

The dosage of APO-BROMAZEPAM (bromazepam) must be individualized and carefully titrated in order to avoid excessive sedation or mental and motor impairment. Short course of treatment should usually be the rule for the symptomatic relief of excessive anxiety and the initial course of treatment should not last longer than one week without reassessment of the need for a limited extension. If necessary, drug dosage can be adjusted after one week of treatment. Initially, not more than one week's supply of APO-BROMAZEPAM should be provided and automatic prescription renewals should not be allowed. Subsequent prescriptions, when required, should be limited to a short course of APO-BROMAZEPAM.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. It is important that the patient should be aware of the possibility of rebound phenomena that may occur while APO-BROMAZEPAM is being discontinued.

Recommended Dose and Dosage Adjustment

Usual Adult Dosage:

The recommended initial adult daily dosage is 6 to 18 mg in equally divided doses, depending on the severity of symptoms and response of the patient. Treatment should be initiated by lower doses and adjusted as necessary. The optimal dosage may range from 6 to 30 mg daily in individual patients, in divided doses. There is limited experience with higher doses up to 60 mg daily.

Geriatrics

Elderly and Debilitated Patients:
Elderly and debilitated patients, or those with organic brain syndrome, have been found to be prone to CNS depression after even low doses of benzodiazepines. Therefore, medication should be initiated in these patients with very low initial doses, and increments should be made gradually, depending on the response of the patient, in order to avoid over sedation or neurological impairment. A reduction in dose for patients above 50 years is recommended.

The initial daily dose in these patients should not exceed 3 mg in divided doses. This dosage can be carefully adjusted, depending on tolerance and response of the patient (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

OVERDOSAGE

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

Symptoms
Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose is seldom life-threatening if APO-BROMAZEPAM 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.

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.

As in overdosage with other benzodiazepines, dialysis is of no known value in bromazepam overdosage.

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: The absolute bioavailability of unchanged, orally administered bromazepam is 60%, and peak blood levels are achieved within 2 hours after administration. Steady state plasma concentrations are reached in around 5 to 9 days. Following multiple oral doses of 3 mg given three times daily, the average maximum concentration of bromazepam at steady-state was 120 ng/mL which is 3- to 4-fold higher than that observed after a single 3-mg dose.

Food may decrease the bioavailability of bromazepam, however, the clinical relevance of this has not been established.

Distribution: On average, 70% of bromazepam is bound to plasma proteins.

Metabolism: Bromazepam is extensively metabolized in the liver. Bromazepam is metabolized, at least in part, through cytochrome P450 (CYP450). However, the specific CYP isozymes involved have not been identified. Nevertheless, the observations that a strong CYP3A4 inhibitor (itraconazole) and a moderate CYP2C9 inhibitor (fluconazole) had no effect on the pharmacokinetics of bromazepam suggest that these isozymes are not involved to a major extent. The pronounced interaction with fluvoxamine points to co-involvement of CYP1A2 (see **DRUG INTERACTIONS, Drug-Drug Interactions**).

Excretion: Bromazepam has an elimination half-life of approximately 20 hours (the half-life may be longer in elderly patients). Over a 72-hour interval, 69% of a 12 mg oral dose was recovered in the urine, in the form of conjugated 3-hydroxybromazepam and conjugated 2-(2-amino-5-bromo-3-hydroxybenzoyl)-pyridine.

Special Populations and Conditions

Geriatrics: Elderly patients may have significantly higher peak concentrations, a smaller volume of distribution, increased serum free fraction, lower clearance and hence also a prolonged elimination half-life of bromazepam. This indicates that steady-state concentrations of bromazepam at any given dosing rate will be on average nearly twice as high in an elderly subject as compared to a younger individual (see **DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment, Elderly and Debilitated Patients**).

Impaired Renal Function: No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with renal impairment.

Impaired Hepatic Function: No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with hepatic impairment.

STORAGE AND STABILITY

Keep APO-BROMAZEPAM stored at room temperature (15°C to 30°C).

SPECIAL HANDLING INSTRUCTIONS

Keep this medicine out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION, AND PACKAGING

APO-BROMAZEPAM 1.5 mg: Each white, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-1.5 on one side) contains 1.5 mg bromazepam. Available in bottles of 100, 250, 500 and 1000.

APO-BROMAZEPAM 3 mg: Each pink, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-3 on one side) contains 3 mg bromazepam. Available in bottles of 100, 250, 500 and 1000.

APO-BROMAZEPAM 6 mg: Each green, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-6 on one side) contains 6 mg bromazepam. Available in bottles of 100, 250, 500 and 1000.

The non-medicinal ingredients are as follows:
APO-BROMAZEPAM tablets contain some or all of the following non-medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose and starch. The following colouring agents are also included: Brilliant Blue Lake 12% (6 mg tablets only), D&C Red #30 Lake 30% (3 mg tablets only), D&C Red #7 Lake 50% (3 mg tablets only), D&C Yellow #10 Lake 16% (6 mg tablets only) and Ferric-ferrous oxide (6 mg tablets only). The 1.5 mg tablets contain no colouring agents.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

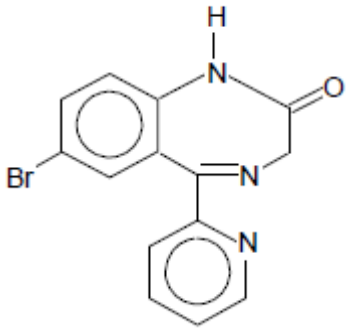
Drug Substance

Proper Name: Bromazepam

Chemical Names: 1) 2*H*-1,4-Benzodiazepin-2-one, 7-bromo-1,3-dihydro-5-(2-pyridinyl)-;

2) 7-Bromo-1,3-dihydro-5-(2- pyridyl)-2*H*-1,4-benzodiazepin-2-one

Structural Formula:



Molecular Formula: $C_{14}H_{10}BrN_3O$

Molecular Weight: 316.16 g/mol

Description: Bromazepam is a practically white, odourless, crystalline powder. It is soluble in acetic acid and dimethylformamide, and is slightly soluble in organic solvents. Bromazepam is insoluble in water. Bromazepam has a melting point of 237 to 240°C.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single dose, blinded, three-way crossover comparative bioavailability study of APO-BROMAZEPAM 1 x 6 mg and 4 x 1.5 mg (Apotex Inc.) and LECTOPAM 1 x 6 mg (Hoffmann-LaRoche Limited) was conducted in healthy adult male volunteers. The results obtained from the 18 subjects that were included in the statistical analyses are presented in the following tables.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bromazepam (1 x 6 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	1574.8 1646.9 (33)	1614.9 1716.0 (38)	97.5	87.3 – 109.0
AUC_I (ng•h/mL)	1797.1 1870.7 (31)	1839.8 1965.5 (42)	97.7	88.0 – 108.4
C_{max} (ng/mL)	71.5 73.8 (28)	73.4 75.4 (23)	97.4	88.3 – 107.5
t_{max}[3] (h)	1.5 (0.5 – 4.0)	1.5 (0.5 – 2.0)		
$T_{1/2}$[4] (h)	20.6 (27)	20.2 (24)		

[1] APO-BROMAZEPAM (bromazepam) tablets 6 mg (Apotex Inc.)
[2] LECTOPAM (bromazepam) tablets 6 mg (Hoffmann-La Roche Limited, Canada)
[3] Expressed as median (range)
[4] Expressed as arithmetic mean (CV%)

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Bromazepam (4 x 1.5 mg vs 1 x 6 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng•h/mL)	1679.9 1801.7 (35)	1614.9 1716.0 (38)	104.0	93.1 – 116.2
AUC_I (ng•h/mL)	1934.3 2078.5 (37)	1839.8 1965.5 (42)	105.1	94.7 – 116.7
C_{max} (ng/mL)	75.5 78.4 (28)	73.4 75.4 (23)	102.8	93.2 – 113.4
t_{max}[3] (h)	1.5 (0.5 – 4.0)	1.5 (0.5 – 2.0)		
$T_{1/2}$[4] (h)	22.0 (26)	20.2 (24)		

[1] APO-BROMAZEPAM (bromazepam) tablets 1.5 mg (Apotex Inc.)
[2] LECTOPAM (bromazepam) tablets 6 mg (Hoffmann-La Roche Limited, Canada)
[3] Expressed as median (range)
[4] Expressed as arithmetic mean (CV%)

DETAILED PHARMACOLOGY

Bromazepam is a benzodiazepine with CNS depressant properties. In laboratory animals, it has shown anti-anxiety, sedative, muscle relaxant and anticonvulsant properties. In a "conflict" test, bromazepam was active in restoring suppressed lever-pressing behaviour (punishment induced suppression) at a minimum effective dose (MED) of 0.16 mg/kg orally in rats. This activity was demonstrated over a dose range which did not involve either depression or stimulation of unpunished control patterns of lever-pressing behaviour. At 2.5 mg/kg, a dose 16 times greater than the MED, bromazepam produced the first decrease in unpunished lever- pressing. In rats, utilizing the Sidman continuous avoidance test, an MED of 1.7 mg/kg i.p. decreased the rate of avoidance of shock and 5.6 mg/kg i.p. prevented the rat from turning off the shock.

A marked reduction in aggressive behaviour was observed in vicious cynomolgus monkeys after an oral dose of 1 mg/kg and a taming effect at a dose of 2.5 mg/kg p.o. In the inclined screen test in mice the ED_{50} for bromazepam was 30 mg/kg p.o. In cats, the minimal effective taming dose of bromazepam was 0.2 mg/kg p.o.

Doses of 0.72 to 0.94 mg/kg p.o. of bromazepam protected mice against metrazol (125 mg/kg) induced convulsions. Bromazepam administered at doses of 3.90 to 34.2 mg/kg and 65 to 133 mg/kg p.o. protected mice against maximal and minimal electroshock-induced convulsions, respectively. A single dose of bromazepam (0.25 to 0.50 mg/kg p.o.) produced sedation or ataxia and modified the sleep cycle in cats. An increase in the amplitude of the electrical patterns of the caudate nucleus was observed.

A decrease in blood pressure was observed after the intravenous administration of bromazepam to anesthetized cats (1 mg/kg) and dogs (5 mg/kg). However, in hypertensive rats, little or no antihypertensive effect was detected. Bromazepam exhibited no diuretic, anti-obesity, anti-diabetic or anti-emetic activity.

Metabolism

The metabolites of bromazepam were studied in the mouse, rat and dog using ^{14}C labelled drug. The quantitative determination of the metabolites indicates that marked differences in the excretion patterns exist in these species. In the mouse and dog, the major metabolite is 3-hydroxybromazepam, although it is only present as a minor metabolite in the rat. Both 2-(2-amino-5- bromobenzoyl) pyridine and its 3-hydroxy derivative are found as metabolites of bromazepam in all three species. In the dog, a separate biotransformation occurs, such that the nitrogen atom, at the 4-position of the diazepam ring, is oxidized to bromazepam 4-oxide. In rats, over 80% of an administered oral dose of bromazepam is excreted in four days, whereas in the dog, excretion is much slower. In rats, biliary excretion and in dogs, urinary excretion is the predominant route of elimination.

TOXICOLOGY

Acute Toxicity:

LD_{50} (mg/kg):

	p.o.	i.p.	s.c.	i.v.
Mice (CFI)	2,350	550	7,400	13.7
Rats – mature (Wistar)	3,050	2,300	-	-
Rats – neonatal	110	-	-	-
(Wistar)	1,690	-	-	-
Rabbits (Wistar)	≥1,280	-	-	-
Dogs				

Signs of toxicity included decreased motor activity, ataxia, loss of righting reflex and lacrimation.

Chronic Toxicity

Bromazepam was administered in the diet to rats for a period of 18 months at doses of 0, 5, 20 and 80 mg/kg/day. No deviations from normal were observed except for an increase in the liver weight at necropsy at the time of the interim kill (18 months). Differences were not found in animals killed at the end of the study (24 months, after 6 months recovery) except for an increase in the ratio of liver to body weight. Histopathological examination revealed centrolobular hepatocellular hypertrophy in the treated groups.

Daily doses of 0, 5, 20 and 80 mg/kg were administered in the diet to dogs for a period of one year. In the high-dose group, untoward effects were slight-to-moderate sedation and ataxia, which decreased as the study progressed. Isolated brief convulsive seizures were observed and an occasional elevation in serum alkaline phosphatase, a borderline increase in SGPT and a slight increase in liver weights occurred in a few dogs in the 80 mg/kg dosage group.

Reproductive Studies

Reproductive, teratological, perinatal and postnatal studies in rats receiving bromazepam at levels of 5 and 50 mg/kg/day p.o. revealed an increase in fetal mortality in the 50 mg/kg group. However, a second reproductive study, in which rats were administered either 10 or 25 mg/kg/day, revealed an increase in the stillbirth rate and a reduction in pup survival at both doses during the first four (4) days following delivery. In another rat study, the daily oral administration of 1 mg/kg, through two successive matings, did not affect the reproductive processes. Bromazepam, at doses of 10 mg/kg/day produced a slight decrease in the number of pregnancies and in the postpartum survival of the offsprings following the second matings. When 100 mg/kg/day was given through three successive matings, a decrease in the number of pregnancies in the parent generation and in the postpartum survivability of the offsprings was observed in all instances. Bromazepam was given to pregnant rabbits at doses of 5 and 50 mg/kg/day administered orally. The following effects were noted: a reduction in maternal weight gain, a reduction in fetal weight and an increase in the incidence of resorptions in both treated groups. In a second study in rabbits, at dose levels of 5 and 80 mg/kg/day p.o., no teratogenic effects were observed. Pregnant mice were administered bromazepam orally, by

stomach tube, from day 7 through 13 or 16 of pregnancy at dose levels of 5, 10, 50 and 125 mg/kg/day. No teratogenic effects were detected.

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PART III: CONSUMER INFORMATION

APO-BROMAZEPAM

Bromazepam Tablets
1.5 mg, 3 mg and 6 mg
Apotex Standard

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

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

ABOUT THIS MEDICATION

What the medication is used for:
The short-term treatment of severe anxiety.

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

What it does:
APO-BROMAZEPAM contains the active ingredient bromazepam, which belongs to a group of medicines known as benzodiazepines. APO-BROMAZEPAM has sedative properties which help in the treatment of severe anxiety.

When it should not be used:
- If you are allergic to the group of medicines known as benzodiazepines (examples: clonazepam, chlordiazepoxide, diazepam, or flurazepam).
- If you are allergic to the medicinal ingredient (bromazepam).
- If you are allergic to any of the other non-medicinal ingredients it contains (see '**What the non-medicinal ingredients are**')
- If you suffer from lung disease or from sleep apnea.
- If you have a liver condition.
- If you have glaucoma.
- If you have myasthenia gravis.
- If a child is less than 18 years of age.

What the medicinal ingredient is:
Bromazepam.

What the non-medicinal ingredients are:
Tablets 1.5 mg:, lactose monohydrate, magnesium stearate, microcrystalline cellulose, starch.

Tablets 3 mg: D&C Red #30 Aluminum Lake 30%, D&C Red #7 Toner Calcium Lake 50%, lactose monohydrate, magnesium stearate, microcrystalline cellulose, starch.

Tablets 6 mg: Brilliant Blue FCF AL Lake 12%, D&C Yellow #10 Aluminum Lake 16%, ferric-ferrous oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose (PH102), starch.

What dosage forms it comes in:
APO-BROMAZEPAM is available as:

1.5 mg tablet – white in colour, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-1.5 on one side).

3 mg tablet - pink in colour, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-3 on one side).

6 mg tablet - green in colour, round, flat-faced, bevelled edge, scored tablet (engraved APO over B-6 on one side).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Addiction, Abuse and Misuse:
Even if you take APO-BROMAZEPAM exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take APO-BROMAZEPAM with:
- **opioids**
- **alcohol or**
- **illicit drugs**

Your doctor should:

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

Store APO-BROMAZEPAM in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking APO-BROMAZEPAM, lower your dose too fast, or switch to another medication, you can experience severe or

life - threatening withdrawal symptoms (see Withdrawal section below).

- **Always contact your doctor before stopping, or lowering your dose of APO-BROMAZEPAM or changing your medicine.**

APO-BROMAZEPAM with Opioids: Taking APO-BROMAZEPAM with opioid medicines can cause:

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

Withdrawal:

- If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop APO-BROMAZEPAM.
- Your risk of going through withdrawal is higher if you are taking APO-BROMAZEPAM for a long time or at high doses. However, symptoms can still occur if you are taking APO-BROMAZEPAM as directed for a short period of time or slowly reducing the dose.
- The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).
- Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment. Severe symptoms of withdrawal include:
  - feeling like you cannot move or respond (catatonia)
  - severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
  - feeling depressed
  - feeling disconnected from reality (dissociation)
  - seeing or hearing things that are not there (hallucinations)
  - overactive behaviour and thoughts (mania)
  - believing in things that are not true (psychosis)
  - convulsions (seizures), including some that do not stop
  - thoughts or actions of suicide

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

- To reduce your chances of going through withdrawal:
  - always contact your doctor before stopping or reducing your dose of APO-BROMAZEPAM or changing medications
  - always follow your doctor's instructions on how to reduce your dose carefully and safely
  - tell your doctor right away if you experience any unusual symptoms after changing or stopping your treatment

APO-BROMAZEPAM with Opioids: Taking APO-BROMAZEPAM with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking APO-BROMAZEPAM

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

Falls and Fractures: there have been reports of falls and fractures in people who take benzodiazepines such as APO-BROMAZEPAM. You have a greater risk of falling, which can cause fractures or other fall related-injuries if you:

- are talking other sedatives (including alcohol),
- are elderly or
- have a condition that causes weakness or frailty

APO-BROMAZEPAM 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-BROMAZEPAM 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 your central nervous system while taking APO-BROMAZEPAM (see INTERACTIONS WITH THIS MEDICATION below).

Memory loss may occur when APO-BROMAZEPAM is used at therapeutic doses.

If you develop any unusual or disturbing thoughts or behaviour while using APO-BROMAZEPAM, 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-BROMAZEPAM may pass 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-BROMAZEPAM talk to your doctor or pharmacist if you:

- have a lung, liver or kidney condition.
- are taking or plan on taking ANY other drugs (including herbal preparations, drugs you purchase without prescriptions, and those not prescribed by your doctor).
- have ever had a problem with:
  - substance use, including prescribed or illegal drugs, or
  - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)
- have a history of depression and/or suicide attempts.
- have the rare hereditary problem of galactose intolerance.
- are pregnant or plan to be pregnant.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

Taking APO-BROMAZEPAM and opioids may cause:

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

Tell your doctor if you are taking any other medicines including any that you have bought from a pharmacy, supermarket or health food store without a prescription.

Some medicines may interfere with APO-BROMAZEPAM. These medicines include:

- medicines to control seizures.
- narcotics and narcotic pain relievers (opioids; see Serious Warnings and Precautions box).
- muscle relaxants.
- sleeping medication.
- antihistamines or allergy medications.
- medicines to treat your mood, such as monoamine oxidase inhibitors, tricyclic antidepressants, phenothiazines.
- Cimetidine, propranolol and fluvoxamine.

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

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

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, kidney or liver function 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	Depending upon severity of symptoms – 6 mg to 18 mg, in equally divided doses. Treatment may be initiated at a lower dose.
Elderly	Maximum of 3 mg in equally divided doses. Dose can be increased 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 dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safety to avoid experiencing withdrawal symptoms.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-BROMAZEPAM, contact a healthcare professional, 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-BROMAZEPAM 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-BROMAZEPAM.

The most common side effects are:
- Feeling drowsy or tired, especially at the start of treatment.
- Loss of some muscle coordination.
- Dizziness.

Less common possible side effects are:
- Rash, nausea, headache, blurred vision, tremors, hypotension (low blood pressure), urinary incontinence, mood disturbances and constipation.
- 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.

Self limiting side effects:
- Falls and fractures

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	Unusual behavioural problems (aggression, rage), sudden anxiety or excitation; restlessness, agitation, irritability; hallucinations (see or hear things that are not there) or delusions; severe sleep disturbances, nightmares, inappropriate behaviour		✓	
	Allergic reactions (red skin, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing, wheezing, shortness of breath, skin rashes, blisters			✓ (Immediately)

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

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
	of the skin, sores or pain in the mouth or eyes)			
	Depression. Symptoms may include: Difficulty sleeping, changes in weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family gatherings and activities with friends, reduced libido (sex drive), and thoughts of death or suicide.		✓	
Unknown	**Overdose:** extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Withdrawal: Severe symptoms include: Catatonia: feeling like you cannot move or respond **Delirium Tremens:** severe confusion,			✓

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
shivering, irregular heartrate and excessive sweating **Feeling depressed Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a			

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

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
burning or prickling feeling in the hands, arms, legs or feet; sweating.			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional

HOW TO STORE IT

- Keep APO-BROMAZEPAM stored at room temperature (15°C to 30°C)
- Keep this medicine out of the sight and reach of children.
- The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided.

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-BROMAZEPAM:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html). Find the Consumer Information on 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,
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