Health Canada Advisories

- New warnings regarding the use of certain sedative and anesthetic drugs during pregnancy and in early childhood. **(2017-12)**

Benzodiazepines

alprazolam—bromazepam—chlordiazepoxide HCl—clobazam—clonazepam—clorazepate dipotassium—diazepam—flurazepam HCl—lorazepam—midazolam HCl—nitrazepam—oxazepam—temazepam—triazolam

Anticonvulsant—Anxiolytic—Hypnotic—Sedative

CPhA Monograph

Date of Revision: May 2015

This monograph has been compiled by CPhA and reviewed by experts. It may contain information different from that found in Health Canada–Approved Product Monographs. The reader is referred to the CPS Editorial Policy for more information.

Summary Product Information

Drug	Route of Administration	Dosage Form	Strength
Alprazolam	Oral	Tablet	0.25 mg, 0.5 mg, 1 mg, 2 mg
Bromazepam	Oral	Tablet	1.5 mg, 3 mg, 6 mg
Chlordiazepoxide HCl	Oral	Capsule	5 mg, 10 mg, 25 mg
Clobazam	Oral	Tablet	10 mg
Clonazepam	Oral	Tablet	0.25 mg, 0.5 mg, 1 mg, 2 mg
Clorazepate dipotassium	Oral	Capsule	3.75 mg, 7.5 mg, 15 mg
Diazepam	Oral	Solution	1 mg/mL; 500 mL
	Oral	Tablet	2 mg, 5 mg, 10 mg
	Rectal	Gel	5 mg/mL
	IM/IV	Injectable solution	5 mg/mL; 2 mL
Flurazepam HCl	Oral	Capsule	15 mg, 30 mg
Lorazepam	Oral	Tablet	0.5 mg, 1 mg, 2 mg
	Sublingual	Tablet	0.5 mg, 1 mg, 2 mg
	IM/IV	Injectable solution	2 mg/mL, 4 mg/mL

Drug	Route of Administration	Dosage Form	Strength
Midazolam HCl	IM/IV	Injectable solution	1 mg/mL; 2, 5, or 10 mL 5 mg/mL; 1, 2, 10 or 50 mL
Nitrazepam	Oral	Tablet	5 mg, 10 mg
Oxazepam	Oral	Tablet	10 mg, 15 mg, 30 mg
Temazepam	Oral	Capsule	15 mg, 30 mg
Triazolam	Oral	Tablet	0.25 mg

Indications and Clinical Use

Benzodiazepines have similar pharmacologic actions; however, clinical uses of specific agents may reflect differences in their pharmacokinetic profiles, the availability of clinical evidence, or the labeled indications for a particular agent.

Health Canada–approved Indications

See Table 1.

Table 1: Health Canada–approved Indications[a]

Drug	Anxiety Disorders	Panic Disorder	Insomnia	Sedation[b]	Seizure Disorders[c]	Skeletal Muscle Spasticity	Alcohol Withdrawal
Alprazolam	Yes	Yes	—	—	—	—	—
Bromazepam	Yes	—	—	—	—	—	—
Chlordiazepoxide	Yes	—	—	—	—	—	—
Clobazam	—	—	—	—	Yes	—	—
Clonazepam	—	—	—	—	Yes	—	—
Clorazepate	Yes	Yes	—	—	Yes	—	Yes
Diazepam	Yes	—	—	Yes	Yes	Yes	Yes
Flurazepam	—	—	Yes	—	—	—	—
Lorazepam	Yes	—	—	Yes	Yes	—	—
Midazolam	—	—	—	Yes	—	—	—
Nitrazepam	—	—	Yes	—	Yes	—	—

Drug	Anxiety Disorders	Panic Disorder	Insomnia	Sedation[b]	Seizure Disorders[c]	Skeletal Muscle Spasticity	Alcohol Withdrawal
Oxazepam	Yes	—	—	—	—	—	Yes
Temazepam	—	—	Yes	—	—	—	—
Triazolam	—	—	Yes	—	—	—	—

[a] Refer to individual product monographs for more detailed information.

[b] Includes pre-operative, pre-procedural sedation, induction of anesthesia or sedation of ventilated patients in an ICU setting.

[c] Used in adults and children.

Uses Without Health Canada Approval

- Benzodiazepines are used in the management of agitation [*West J Emerg Med* 2012;13(1):26-34], restless legs syndrome [*Eur Neuropsychopharmacol* 2001;11(2):153-61], skeletal muscle spasticity and alcohol withdrawal [*Clin Pharmacol Ther* 1983;34(2):214-9]; they are also used adjunctively prior to surgical or diagnostic procedures or in the management of some psychiatric disorders, nausea and vomiting associated with cancer chemotherapy [*Ann Oncol* 2010;21(Suppl 5):v232-43] or end-of-life dyspnea with an anxiety component [*Cochrane Database Syst Rev* 2010;20(1):CD007354]. Some benzodiazepines (e.g., clonazepam, lorazepam) are used to treat panic disorder.

Contraindications

- Patients with known hypersensitivity to this class of drugs or to any component of the product in question. Manufacturers advise against the use of benzodiazepines in patients with myasthenia gravis and acute angle-closure glaucoma, but they may be used in patients receiving appropriate therapy for open-angle glaucoma.

Warnings and Precautions

Serious Warnings and Precautions

- Benzodiazepines should be used with extreme caution in patients with severe pulmonary insufficiency or sleep apnea, especially in patients who are elderly, very ill or who have limited pulmonary reserve.
- Resuscitative facilities and equipment should be available when benzodiazepines are administered parenterally and, in particular, by the iv route. These agents should not be administered iv to patients who are in shock or a coma, show signs of acute alcohol intoxication, or who have recently received other respiratory depressant drugs.
- Benzodiazepines should be used with caution in patients who are severely depressed or show any sign of impending depression with an associated anxiety disorder, particularly patients at risk of increased suicidal tendencies. Appropriate protective measures may be necessary during benzodiazepine therapy in these patients. Careful consideration should be given to the quantity of medication prescribed at any one time.
- Patients should be informed about possible negative effects on memory and advised to report any mental or behavioral changes that develop during benzodiazepine therapy to their physician.
- Health Canada issued an advisory in October 2009 to make patients and clinicians aware of cases where patients took a sedative-hypnotic agent and subsequently engaged in activities such as driving, making phone calls or cooking/eating meals while not fully awake, and with no recall of the event(s). The risk of such events is increased when benzodiazepines are used in higher than recommended sedative doses or used concurrently with alcohol or other CNS depressants. The advisory applies to benzodiazepines officially indicated as hypnotics (i.e., flurazepam, nitrazepam, temazepam and triazolam) and the nonbenzodiazepines, zolpidem and zopiclone. In light of the safety implications of engaging in potentially

hazardous activities such as driving while not fully awake, consider discontinuing the benzodiazepine in any patient who experiences this type of event.

General

Benzodiazepine therapy should be individualized and closely monitored, and the need for continued therapy should be re-evaluated frequently, especially in the elderly. Long-acting benzodiazepines (chlordiazepoxide, clorazepate, diazepam and flurazepam) and triazolam should be avoided in elderly patients.

Dependence and Withdrawal

Tolerance and the risk of psychological and physical dependence may occur following prolonged use of benzodiazepines at therapeutic doses. Such effects also may occur following short-term use of benzodiazepines, particularly at higher doses. Tolerance to the hypnotic and sedative effects develops rapidly. In contrast, even after prolonged use, clinically significant tolerance to the anxiolytic effect does not usually occur. Risk of benzodiazepine dependence can be minimized by initial screening of the patient for possible risk factors, patient education, dose titration along with close observation for effects and follow-up as appropriate.

Benzodiazepine use should be avoided in patients with a history of alcohol or substance abuse, except for the treatment of acute alcohol withdrawal.

Abrupt withdrawal of benzodiazepines may lead to symptoms such as anxiety, insomnia, psychomotor agitation, GI discomfort, hand tremor, anorexia, diaphoresis, tachycardia, photophobia or phonophobia. More severe symptoms may occur such as confusion, depersonalization, myoclonus, delirium, psychosis or seizures. Rebound insomnia may occur, particularly following abrupt discontinuation of a benzodiazepine with a short elimination half-life.

Dosage tapering or inadvertent discontinuation (e.g., forgotten doses on admission to hospital) can precipitate withdrawal. Such effects can also emerge in the early morning following bedtime administration of a short-acting agent. In addition, an increase in daytime anxiety and/or restlessness may occur between doses of short-acting agents. Rebound or re-emergence of symptoms may occur after as little as 4–6 weeks of therapy and are more likely if the drug is short-acting, taken regularly for >3 months and abruptly discontinued. Symptoms may be similar or more intense than those experienced by the patient prior to initiation of the benzodiazepine.

Choice of withdrawal regimen may depend on the setting of detoxification, severity of dependence and concurrent drug or substance abuse. Patients should follow a structured discontinuation program. In patients on prolonged benzodiazepine therapy, dosage should be gradually decreased over about 6–12 weeks, especially in patients with a history of seizures or epilepsy, regardless of their concomitant antiepileptic drug therapy. For patients taking a short-acting agent, substitution with a longer-acting benzodiazepine may provide a gradual decrease in drug concentration and reduce the possibility of withdrawal symptoms. For patients who are taking ≥60 mg of diazepam daily or who have a history of serious withdrawal reactions, consider hospitalization during acute withdrawal with more gradual dosage tapering than in those managed as outpatients.

Hematologic

There have been isolated reports of blood dyscrasias; periodic blood counts may be of benefit during long-term therapy.

Hepatic/Biliary/Pancreatic

There have been isolated reports of abnormal liver function tests; periodic liver function tests may be of benefit during long-term therapy. Patients with hepatic impairment should be monitored and the dose carefully titrated to avoid accumulation.

Neurologic

Elderly or debilitated patients, children, and patients with liver disease or low serum albumin are most likely to experience CNS adverse effects. To minimize the possibility of ataxia, dizziness and oversedation, it is generally recommended that therapy be initiated with low dosages and gradually titrated to the lowest effective dose.

Neonates can experience prolonged CNS depression because of their inability to convert benzodiazepines to inactive metabolites.

There is some evidence that ataxia and the risk of falling and associated hip fracture in elderly patients is greatest with the use of long-acting benzodiazepines compared with short-acting agents. Differences in the degree of residual and cumulative CNS depressant effects among the benzodiazepines may be particularly important in elderly patients, in patients with potentially impaired elimination of drugs and in individuals whose occupation or lifestyle requires unimpaired intellectual or psychomotor function.

Anterograde amnesia has occurred following therapeutic doses of benzodiazepines. The severity and duration of this effect may vary depending on the drug, dosage, route of administration or individual patient, e.g., elderly patients may be at particular risk. Although amnesic effects have been more commonly associated with midazolam, triazolam and lorazepam, these effects have occurred with other benzodiazepines. Data suggest that anterograde amnesia and next-day memory loss occur at a higher rate with triazolam, generally at a 0.5 mg dose. Cases of transient global amnesia and “traveler's amnesia” have been reported in patients taking triazolam to induce sleep while traveling. These amnesic effects are unpredictable and not necessarily dose related. Advise patients not to take triazolam when a full night's sleep is not possible, e.g., an overnight flight of less than 7–8 hours, otherwise drug clearance from the body may be incomplete and impair the patient's alertness and ability to resume full activity.

Psychiatric

Paradoxical CNS stimulation such as restlessness, anxiety, mania, insomnia, sleep disturbances, increased muscle spasticity, acute rage and hyperactivity has been reported with benzodiazepines in patients with psychiatric disorders and hyperactive, aggressive children. These reactions have appeared early in therapy, usually in the first 2 weeks. If CNS stimulation occurs, benzodiazepine therapy should be discontinued.

Serious behavioural changes and abnormal thinking have occasionally been associated with benzodiazepine use and are similar to those seen with alcohol and other CNS depressants. Examples include hallucinations, depersonalization, agitation, bizarre behavior and decreased inhibition manifested as aggression or excessive extroversion.

Reversible dementia has also been reported in the elderly after prolonged administration of benzodiazepines.

Renal

Patients with renal impairment should be monitored and the dose carefully titrated to avoid accumulation.

Special Populations

Pregnant Women

Benzodiazepines should generally be avoided during pregnancy. Benzodiazepines freely cross the placenta and accumulate in the fetal circulation, and may be associated with a slightly increased risk of congenital malformations following first-trimester exposure. Hypotonia, lethargy and sucking difficulties have been reported in infants whose mothers received benzodiazepines close to delivery. Chronic use of benzodiazepines during pregnancy has also been associated with neonatal withdrawal. The use of benzodiazepines solely for hypnotic effect is contraindicated during pregnancy. In the management of a seizure disorder during pregnancy, the risk of continued benzodiazepine therapy must be weighed against the risk of discontinuation and the lowest effective dose should be used. Avoid abrupt discontinuation.

Nursing Women

Benzodiazepines are excreted in breast milk and neonates have limited ability to metabolize these drugs. Intermittent, short-term use of benzodiazepines is considered relatively safe in breastfeeding women. However, when taken chronically by the mother the drugs can accumulate in a nursing infant. Theoretically, the use of shorter-acting agents with low lipophilicity and no active metabolites, such as oxazepam and lorazepam, may be preferable.

Pediatrics

Some benzodiazepines have pediatric indications that are similar to those for adults. Precautions are the same for both pediatric and adult patients, but benzodiazepines can cause paradoxical excitation in children. Specialized references should be consulted for detailed information.

Geriatrics

See also General, Neurologic, Psychiatric and Occupational Hazards.

Caution is advised if benzodiazepines are administered parenterally to elderly patients; these patients have a higher risk of experiencing apnea, hypotension, bradycardia or cardiac arrest.

Chlordiazepoxide, clorazepate, diazepam, flurazepam and triazolam are not recommended in elderly patients. See Warnings and Precautions.

Occupational Hazards

Benzodiazepines have a CNS depressant effect. Patients taking benzodiazepines should be warned about a potential impairment of mental alertness or physical coordination that can affect their ability to perform hazardous tasks such as driving or operating machinery. Elderly patients may be at particular risk for these CNS depressant effects, potentially predisposing them to falls or motor vehicle accidents.

Adverse Reactions

More Common Adverse Drug Reactions (≥1%)

See Table 2. Dose-dependent CNS effects are the most commonly reported adverse effects of benzodiazepines.

Table 2: More Common Adverse Drug Reactions (≥1%)

Body System	Effect	Clinical Comment
Central Nervous System	Ataxia	Usually occur in first few days of treatment and may decrease with continued therapy. Can be partially prevented by starting with low doses and slowly increasing to the lowest effective dose. If effects persist, consider a dosage reduction. Elderly or debilitated patients, children, and patients with liver disease or low serum albumin may be unusually sensitive to the CNS effects.
	Dizziness	
	Drowsiness, including residual daytime drowsiness	
	Fatigue	
	Muscle weakness	
	Slowed reaction	

Less Common Adverse Drug Reactions (<1%)

Cardiovascular

hypotension, palpitations, phlebitis, syncope, tachycardia, venous thrombosis.

Central Nervous System

behavioural problems, memory impairment, mental depression, paradoxical stimulant reactions, withdrawal syndrome.

Gastrointestinal

abdominal or stomach cramps/pain, constipation, diarrhea, dry mouth, increased thirst, increased salivation, jaundice, nausea, vomiting.

Genitourinary

incontinence, urinary retention.

Hematologic

leukopenia, thrombocytopenia.

Immune

hypersensitivity reactions.

Neurologic

confusion, euphoria, headache, muscle spasms, seizures, slurred speech, vertigo, vivid or disturbing dreams, trembling, unusual tiredness or weakness.

Ophthalmologic

blurred vision, diplopia.

Respiratory

apnea, increased bronchial secretions, respiratory depression.

Sexual Function

sexual dysfunction.

Drug Interactions

Drug-Drug Interactions

See Table 3.

Table 3: Drug-Drug Interactions

Interacting Drug	Effect	Clinical Comment

Interacting Drug	Effect	Clinical Comment
CNS depressants (e.g., alcohol, anesthetics, antidepressants, antipsychotics, hypnotics, opioids, sedating antihistamines)	Additive CNS depressant effects. Chronic alcohol use may result in early tolerance to benzodiazepines. Concomitant administration with opioids may lead to enhanced euphoria and psychological dependence. Increased risk of complex sleep-related behaviours such as sleep-driving (see Warnings and Precautions).	Avoid combination when possible. Monitor for increased CNS depressant effects. Warn patients about possible effects of combining medications with alcohol or other sedatives.
Inhibitors of CYP3A4 (e.g., diltiazem, fluoxetine, fluvoxamine, isoniazid, macrolide antibiotics, protease inhibitors, verapamil)	Increased serum concentrations and effects of benzodiazepines (e.g., increased and prolonged sedation) metabolized by the affected enzyme (see Table 5).	Monitor for increased effects of benzodiazepines. Reduce dose of benzodiazepine accordingly.
Inducers of CYP3A4 (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, valproate)	Decreased serum concentrations and effects of benzodiazepines metabolized by the affected enzyme[a] (see Table 5).	Monitor for decreased efficacy of benzodiazepines. Adjust dose accordingly.
Inhibitors of CYP2C19 (e.g., fluconazole, ketoconazole, omeprazole, oral contraceptives, ticlopidine)	Increase in pharmacologic effects of benzodiazepines metabolized by the affected enzymes (see Table 5).	Monitor for increased effects of benzodiazepines. Adjust dose accordingly.

[a] Cigarette smoking may have a similar effect on benzodiazepines. Polycyclic aromatic hydrocarbons in tobacco smoke induce CYP1A2, a hepatic enzyme responsible for the metabolism of many drugs.

Drug-Food Interactions

Grapefruit, Seville oranges, pomelos and limes can increase serum levels of diazepam and triazolam. Avoid the combination of these fruits and agents. If unavoidable, decrease the benzodiazepine dosage. Alprazolam is known not to interact with grapefruit while lorazepam, oxazepam and temazepam are predicted not to interact.

Drug-Herb Interaction

St. John's wort is a CYP3A4 inducer and will decrease the serum level and effect of benzodiazepines metabolized by this enzyme (see Table 5).

Dosage and Administration

Benzodiazepine dosages should be individualized and titrated carefully to avoid excessive sedation and mental or motor impairment. Use the lowest effective dose and reassess the need for continued therapy frequently. Higher doses and longer treatment duration may increase the risk of dependence. Some individual product monographs recommend maximum duration of use or maximum quantity per prescription, e.g., in the treatment of insomnia or anxiety. Oral dosages for the more common indications for each agent are included in Table 4.

Please refer to individual product monographs or other specialized references for dosage recommendations for specific patient groups such as children, elderly or debilitated patients, or those with hepatic or renal failure, or for indications not included in the table.

Recommended Dose and Dosage Adjustment

Adults

See Table 4.

Table 4: Oral Dose for Common Indications in Adult Patients

Drug	Indication	Usual Dose[a]
Alprazolam[a]	Anxiety	0.25–0.5 mg TID
	Panic disorder	0.5 mg TID
Bromazepam[a]	Anxiety	Initial: 6–18 mg/day in divided doses Usual maintenance range: 6–30 mg/day
Chlordiazepoxide[b]	Anxiety	5–25 mg TID–QID
Clobazam[a]	Seizure disorders	Initial: 5–15 mg/day, preferably HS Maintenance: 20–40 mg/day, in 1–2 divided doses
Clonazepam[a]	Anxiety, Panic disorder	0.25–0.5 mg BID
	Seizure disorders	Initial: 0.5 mg TID; increase by 0.5–1 mg daily every 3 days as needed and tolerated Maximum: 20 mg/day
Clorazepate[b]	Anxiety	7.5–15 mg BID–QID *or* single dose of 15–22.5 mg HS
	Seizure disorders	Initial: Up to 7.5 mg BID–TID; increase by no more than 7.5 mg per week, to a maximum of 90 mg/day
Diazepam[b]	Anxiety/Seizure disorders	2–10 mg BID–QID
Flurazepam[b]	Insomnia	15–30 mg HS
Lorazepam[a]	Insomnia	0.5–1 mg HS
Nitrazepam[a]	Insomnia	5–10 mg HS
Oxazepam[a]	Anxiety	10–30 mg TID–QID
	Insomnia	15 mg 30–60 minutes before bedtime
Temazepam[a]	Insomnia	15–30 mg HS
Triazolam[b]	Insomnia	0.125–0.25 mg HS

[a] Dose provided is for healthy younger adults. Elderly patients may be particularly sensitive to the CNS effects of benzodiazepines. With decreased hepatic metabolism, benzodiazepines may have longer elimination half-lives. In general, dosages for elderly patients should be approximately one-third to one-half of the recommended dose for younger adults.

[b] Not recommended in elderly patients.

Geriatrics

Elderly patients may be particularly sensitive to the CNS effects of benzodiazepines. With decreased hepatic metabolism, benzodiazepines may have longer elimination half-lives. In general, dosages for elderly patients should be approximately one-third to one-half of the recommended dose for younger adults. Diazepam, flurazepam and triazolam are not recommended in elderly patients.

Dialysis

Benzodiazepines are not significantly removed by dialysis.

Overdosage

For management of a suspected drug overdose, contact your regional Poison Control Centre. See the eCPS Directory section for a list of Poison Control Centres.

Signs and Symptoms

Symptoms of mild overdose include drowsiness, impaired coordination, diminished reflexes, confusion and lethargy. In more serious overdose, symptoms may include ataxia, hypotonia, hypotension, respiratory depression and coma. Although cardiac arrest has been reported, death from overdose of benzodiazepines in the absence of concurrent ingestion of alcohol or other CNS depressants is rare.

Recommended Management

Management consists of appropriate supportive therapy and symptomatic management. Assess for possible co-ingestion of other substances. Activated charcoal (about 1 g/kg) may be administered for a recent (<60 minutes), large oral benzodiazepine overdose, as long as the patient is sufficiently alert to adequately protect their airway. Vital signs and fluid balance should be monitored. Ensure that an adequate airway is maintained and respiration is assisted as required. Hypotension is not generally problematic and is usually managed with boluses of isotonic iv fluids.

Flumazenil is a benzodiazepine antagonist that should be used very cautiously, ideally after consultation with a Poison Control Centre. Potential candidates are patients with severe benzodiazepine toxicity or overdose who are not benzodiazepine-dependent and who have not consumed proconvulsant drugs. Flumazenil is *contraindicated* in any patient who might have co-ingested a tricyclic antidepressant or used benzodiazepines chronically. Sudden benzodiazepine reversal by flumazenil in patients taking chronic doses can induce withdrawal and precipitate seizures.

Flumazenil is generally reserved for the management of severely symptomatic pure benzodiazepine overdose. Flumazenil should only be administered when continuous monitoring for recurrence of sedation can be assured. Flumazenil rapidly reverses the hypnotic-sedative effects of benzodiazepines. However, the residual effects may reappear gradually within a few hours, depending on the dose of flumazenil, the time elapsed since the benzodiazepine was administered, and elimination half-life of the benzodiazepine in question. Flumazenil's effects on respiratory depression are inconsistent; in some studies residual respiratory depressant effects were still present despite reversal of sedation. Improved consciousness is expected within the first several minutes of flumazenil administration, but ventilatory support may be required for respiratory depression. Flumazenil does not consistently reverse benzodiazepine-associated amnesia. Consult the flumazenil product monograph for complete prescribing information.

Dialysis is of limited value in benzodiazepine overdose.

Action and Clinical Pharmacology

Mechanism of Action

Benzodiazepines exhibit an affinity for benzodiazepine receptors that act as specific binding sites for gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS. Benzodiazepines are believed to produce their CNS effects by interacting with a macromolecular protein complex in the neuronal membrane that includes $GABA_A$ receptors, high-affinity benzodiazepine receptors and chloride channels.

Benzodiazepines with very similar chemical structures can differ in their potency, rate of absorption and other pharmacokinetic parameters. The potency of a benzodiazepine is correlated with its affinity for its binding site, the benzodiazepine receptor. In therapeutic use, the benzodiazepines have similar pharmacologic profiles but differ in potency.

Different types of benzodiazepine receptors in various areas of the CNS are thought to produce the different pharmacologic actions of the drugs. As the dose of benzodiazepine is increased, anxiolytic effects are first produced, followed by anticonvulsant effects, a reduction in muscle tonus, and finally sedation and hypnosis.

Pharmacokinetics

When selecting appropriate benzodiazepine therapy, consider the different pharmacokinetic properties of each agent. Table 5 lists the major pharmacokinetic properties of these agents.

Benzodiazepines are widely distributed in the body and accumulate preferentially in lipid rich areas such as the CNS and adipose tissue. The more lipophilic agents have the fastest rates of absorption and onset of clinical effects. Benzodiazepines and their metabolites are highly bound to plasma proteins (80–99%).

Steady state plasma concentrations of benzodiazepines and their metabolites are reached after about 5 elimination half-lives, ranging from a few days to 2 weeks after initiation of therapy.

Drug accumulation and prolonged effects can occur with chronic dosing of benzodiazepines or active metabolites with very long elimination half-lives. This is especially important in patients who are elderly or obese, have liver disease or take other drugs that compete for hepatic oxidation. Benzodiazepines that are metabolized by hepatic glucuronide conjugation and do not have active metabolites are unlikely to accumulate with chronic administration and will require multiple daily dosing for sustained effects.

Most benzodiazepines are excreted almost entirely in the urine in the form of oxidized and glucuronide-conjugated metabolites. Benzodiazepines are not significantly removed by hemodialysis.

Table 5: Pharmacokinetic Properties[a,b]

Drug	Approximate Equivalent Oral Dose (mg)	Time to Peak Concentration (hours)	Onset of Action[c]	Active Metabolites	Pathway of Metabolism	Approximate Half-life (hours, parent compound and active metabolite)
Long-acting						
Chlordiazepoxide	10	0.5–4	I	Yes	Oxidation (CYP1A2)	100
Clorazepate	7.5	0.5–2	F	Yes	Oxidation	100

Drug	Approximate Equivalent Oral Dose (mg)	Time to Peak Concentration (hours)	Onset of Action[c]	Active Metabolites	Pathway of Metabolism	Approximate Half-life (hours, parent compound and active metabolite)
Diazepam	5	Oral: 0.5–2 h Rectal gel: 1.5 h IM: 1 h (erratically absorbed)	F	Yes	Oxidation (CYP1A2, 2C9, 2C19, 3A4)	100
Flurazepam	15	0.5–1	F	Yes	Oxidation (CYP2C9, 3A4)	100
Intermediate-acting						
Alprazolam	0.5	1–2	I	Yes	Oxidation (CYP3A4)	12–15
Bromazepam	3	1–4	I	Yes	Conjugation	8–30
Clobazam	10	1–4	I	Yes	Oxidation	10–46
Clonazepam	0.25	1–2	I	No	Oxidation (CYP3A4); reduction	20–60
Lorazepam	1	Oral: 2–4 h IM: 45–75 min IV: 5–10 min Sublingual: 1 h	I	No	Conjugation	10–20
Nitrazepam	5	2–3	I	No	Reduction (CYP2E1)	16–55
Oxazepam	15	2–4	S	No	Conjugation	5–25
Temazepam	10	2–3	I	No	Conjugation	10–20
Short-acting						
Midazolam[d]	Not applicable	See Onset of Action	IM: 5–15 min IV: 1.5–5 min[e]	Yes	Oxidation (CYP3A4)	1–4
Triazolam	0.25	1–2	F	No	Oxidation (CYP3A4)	1.5–5

[a] After oral administration, unless otherwise indicated.

[b] Gender, age, hepatic and renal impairment can influence properties of individual agents.

[c] Legend: F=fast (<1 h); I=intermediate (1–3 h); S=slow (>3 h).

[d] Parenteral use only.

[e] Onset of action may be faster if opioid administered concurrently.