

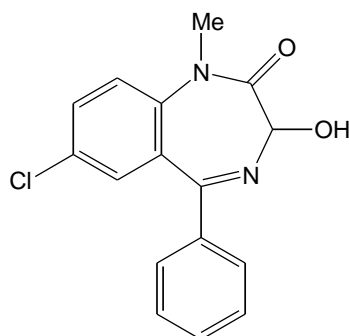
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active Ingredient: Temazepam

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

Structural formula:



Molecular formula: $C_{16}H_{13}ClN_2O_2$

Molecular weight: 300.7

CAS Registry no.: 846-50-4

DESCRIPTION

Temazepam is a white or almost white, odourless crystalline powder. It is sparingly soluble in ethanol 96% and freely soluble in dichloromethane, but is practically insoluble in water.

Each Temaze tablet contains 10 mg of temazepam. The tablets also contain lactose, maize starch, microcrystalline cellulose and magnesium stearate.

PHARMACOLOGY

Temazepam is a benzodiazepine derivative which hastens the onset of sleep and increases total sleeping time in short term use.

The exact mechanism of action of benzodiazepines has not yet been elucidated, however, benzodiazepines appear to work through several mechanisms. Benzodiazepines presumably exert their effects by binding to specific receptors at several sites within the central nervous system either by potentiating the effects of synaptic or pre-synaptic inhibition mediated by gamma-aminobutyric acid (GABA), or by directly affecting the action potential generating mechanisms.

Pharmacokinetics

Pharmacokinetic studies have shown that temazepam is well absorbed and has a relatively short elimination half-life of approximately 10 hours (range 5 – 15 hours). Peak plasma levels of the drug occur 30 to 120 minutes after administration of the tablets. With multiple dosing, steady state is obtained by the third day, and there is little or no accumulation of parent drug or metabolites.

Temazepam is metabolised principally in the liver where most drug is directly conjugated to the glucuronide and excreted in the urine. Some drug is demethylated to oxazepam and eliminated as the glucuronide. The

glucuronides of temazepam have no demonstrable CNS activity. Following a single oral dose, 80% of the dose appears in the urine, mostly as the conjugates, and 12% of the dose appears in the faeces. Less than 2% of the dose is excreted unchanged in the urine. Approximately 96% of unchanged drug is bound to plasma proteins.

INDICATIONS

Temaze is indicated for:

- Adjunctive therapy in the short term management of insomnia in adults.

CONTRAINDICATIONS

Temaze is contraindicated in:

- Patients with a known hypersensitivity to benzodiazepines or to any of the components of the formulation.
- Patients with chronic obstructive airways disease with incipient respiratory failure.
- Patients with sleep apnoea.

Temazepam should not be used as monotherapy to treat depression, or symptoms of anxiety associated with depression, due to a risk of suicide (see **PRECAUTIONS**).

PRECAUTIONS

Hypotension

Although hypotension has occurred rarely, Temaze should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Myasthenia gravis

Temazepam could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Acute narrow-angle glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired renal/liver function and blood dyscrasia

Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended. The use of temazepam may worsen hepatic encephalopathy; therefore, temazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy.

Depression, psychosis and schizophrenia

Temaze is not recommended as primary therapy in patients with depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients, and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered, and protective measures may be required.

CNS and/or Paradoxical reactions

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been described.

- Amnesic symptoms: anterograde amnesia with appropriate or inappropriate behaviour;
- Confusional states: disorientation, derealisation, depersonalization and/or clouding of consciousness; and
- Agitational states: sleep disturbances, restlessness, irritability, aggression and excitation.

Temazepam should be discontinued if confusion or agitation occurs.

Paradoxical reactions such as acute rage, stimulation or excitement may occur; should such reactions occur, Temaze should be discontinued. Such reactions may be more likely to occur in children and the elderly.

Elderly or debilitated patients

Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall. Temaze 10 mg is the recommended starting dose for these patients.

Impaired respiratory function

Use of benzodiazepines, including temazepam, may lead to potentially fatal respiratory depression. Caution in the use of Temaze is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased arterial oxygen tension.

Epilepsy

Abrupt withdrawal of benzodiazepines in patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Abuse

Caution must be exercised in administering Temaze to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence

The use of benzodiazepines, including temazepam, may lead to physical and psychological dependence as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with higher doses and longer term use and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. Temazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Duration of Treatment

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). Continuous long-term use of Temaze is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Tolerance

Tolerance as defined by a need to increase the dose in order to achieve the same therapeutic effect seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines especially in those with drug seeking behaviour.

Withdrawal

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms can range from headache, nausea, diarrhoea, loss of appetite, insomnia, anxiety, tensions, depression, restlessness, irritability, rebound phenomena, dysphoria, dizziness, abdominal cramps, agitation, palpitations, tachycardia, panic attacks, vertigo, myoclonus akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), depersonalisation, derealisation, hyperacusis, delusional beliefs, hyperreflexia, numbness/tingling of extremities and loss of short term memory, to a major syndrome which may include convulsions/seizures, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the seizure threshold such as antidepressants. Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, Temaze should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses taken for relatively short periods.

Dose Tapering

Following the prolonged use of Temaze at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of Temaze (see Precautions - Dependence).

Somnambulism and associated behaviours

Complex behaviours such as “sleep-driving” (i.e. driving while not fully awake after taking a sedative-hypnotics, with amnesia for the event) have been reported with sedative hypnotics. These events can occur in sedative-hypnotics naive as well as in sedative-hypnotic experienced persons. These events can occur at normal therapeutic doses, and the risk appears to be increased when sedative-hypnotics are combined with alcohol or other CNS depressants or used at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of sedative-hypnotics should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviours (eg. preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events.

Angioedema

Angioedema involving the tongue, glottis and larynx has been reported in some patients after taking the first or subsequent doses of sedative-hypnotics. These cases of angioedema may cause airway obstruction and be fatal; this has required medical therapy in emergency departments for some patients. Additional symptoms have been reported in some patients including dyspnea, throat closing, or nausea and vomiting suggesting anaphylaxis.

Concomitant use with Alcohol/CNS Depressants

The concomitant use of Temazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Temazepam which may include severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see **INTERACTIONS WITH OTHER MEDICINES**).

Effects on Fertility

In animal studies, an increased perinatal mortality has been seen following concomitant administration of temazepam and diphenhydramine to rabbits in the later stages of gestation compared with rabbits that received either drug alone. It is recommended that the use of temazepam be avoided in pregnant women receiving antihistamines.

Fertility in male and female rats was not adversely affected by temazepam.

Use in Pregnancy (Category C)

Temazepam should not be used during pregnancy.

Benzodiazepines cross the placenta and may cause hypoactivity, hypotonia, reduced respiratory function, apnoea, feeding problems, hypothermia and impaired metabolic response to cold stress in the newborn infant of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

The use of benzodiazepines during the first trimester of pregnancy should almost always be avoided. An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects that she is pregnant.

Non-teratogenic effects

The use of benzodiazepines during the last phase of pregnancy or at delivery may require ventilation of the infant at birth.

Use in Lactation

Caution should be exercised when Temaze is given to breast feeding women.

Temazepam is believed to be excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant.

Paediatric Use

The safety and effectiveness of temazepam has not been established in children less than 16 years of age.

Effects on Laboratory Tests

No interference with laboratory tests have been identified or reported with the use of temazepam.

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, have been reported with benzodiazepine administration.

Effects on Ability to Drive and Use Machinery

As with all patients taking CNS depressant medications, patients receiving Temaze should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from Temaze therapy. Abilities may be impaired on the day following use. In sleep laboratory studies in volunteers, doses of 10 and 20 mg did not significantly affect morning performance, however the 30 mg dose produced impairment of psychomotor behaviour on the morning following night time administration. Discontinuation of Temaze is highly recommended for patients who report a “sleep-driving” episode (see **Somnambulism and associated behaviour**).

INTERACTIONS WITH OTHER MEDICINES

CNS Depressants

The benzodiazepines, including temazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics.

Cytochrome P450

The cytochrome P450 system has not been shown to be involved in the disposition of temazepam and, unlike many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with temazepam.

Anticonvulsants

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

Theophylline/Aminophylline

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines.

Potential of Anticholinergic Effects

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

ADVERSE EFFECTS

All adverse reactions reported with temazepam are common with other benzodiazepine compounds.

More common reactions

Nervous system:

dizziness, headache, vertigo, sedation, fatigue, drowsiness, ataxia

Less common reactions**Body as a whole:**

asthenia

Biochemical:

elevated SAP, AST, BUN, bilirubin; proteinuria, neutrophil, leucocytosis

Cardiovascular:

palpitation, tachycardia

Dermatological:

allergic skin reactions including macular rash and pruritus

Gastrointestinal:

dry mouth, nausea, vomiting, gastrointestinal upset

Musculoskeletal:

leg cramps, weakness

Nervous system:

confusion, disorientation, muzziness, sciatica, tremor, faintness, change in libido, impotence, decreased orgasm

Ocular:

blurred vision

Respiratory:

breathlessness

Psychiatric:

unmasking of depression, irritability, vivid dreams

Miscellaneous:

loss of taste

Frequency undetermined

Body as a whole:

hypersensitivity reactions, anaphylactic/oid reactions, SIADH (syndrome of inappropriate antidiuretic hormone secretion), hyponatraemia, hypothermia.

Cardiovascular:

hypotension, lowering in blood pressure.

Digestive:

constipation, jaundice.

Haematological/Lymphatic:

thrombocytopaenia, agranulocytosis, pancytopaenia.

Nervous system and special senses:

extrapyramidal symptoms, visual disturbance (including diplopia), dysarthria/slurred speech, convulsions/seizures, amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt (benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with higher doses).

Respiratory:

respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with higher doses), worsening of obstructive pulmonary disease.

Dermatological:

alopecia.

Paradoxical reactions such as anxiety, agitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations, stimulation and excitement rarely occur (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Dosage should be individualised for maximum beneficial effect. For use as a hypnotic, the usual adult dose is 10 to 30 mg, taken one-half hour before retiring. In elderly or debilitated patients, 10 mg Temaze is the initial recommended dosage (see **PRECAUTIONS - Elderly or debilitated patients**).

The need for continued therapy with Temaze in patients who have been taking medication for several weeks should be evaluated periodically.

Temaze is not recommended for children.

OVERDOSAGE

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, lethargy, dysarthria and paradoxical reactions. In more serious cases, symptoms may include ataxia, CNS depression, hypotonia, hypotension, respiratory depression, cardiovascular depression, coma, and very rarely proves fatal.

Treatment:

In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken. Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdose.

Following overdosage with oral benzodiazepines, activated charcoal may be given to reduce absorption, if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

PRESENTATION AND STORAGE CONDITIONS

Temaze

Temazepam 10 mg tablet: 5.5 mm flat bevel edged white to off-white tablet, debossed "TE" on one side and "α" on the other. 10

Available in blister packs (PVC/PVDC/Al) or bottles (HDPE bottle with PP cap)* of 25's*, 30's and 50's.

* Marketed in Australia.

Store below 30°C. Store in original container. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13/05/1998

DATE OF MOST RECENT AMENDMENT

02/12/2014

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