AUSTRALIAN PRODUCT INFORMATION

TEMAZE®

(temazepam) tablets

1 NAME OF THE MEDICINE

Temazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Temaze tablet contains 10 mg of temazepam.

Excipients with known effect: Sugars as lactose. Also contains traces of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

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

Blisters: Temazepam 10 mg tablet: 5.5 mm flat bevel edged light orange tablet, debossed TE over 10 on one side, alpha symbol on the other

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Temaze is indicated for:

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

4.2 DOSE AND METHOD OF 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - 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.

4.3 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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).

Blood dyscrasia

In rare instances some patients taking benzodiazepines have developed blood dyscrasias. As with other benzodiazepines, periodic blood counts are recommended.

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.

- Amnestic 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - 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 dyspnoea, 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 Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Concomitant use with Opioids

Concomitant use of temazepam and opioids may result in sedation, respiratory depression, coma and death. Due to these risks, concomitant prescribing of temazepam with opioids should be reserved for patients when alternative treatment options are not possible. If a decision is made to prescribe temazepam concomitantly with opioids, the lowest effective dose should be used for the shortest duration possible. The patient should be monitored closely for signs and symptoms of respiratory depression and sedation. The patient and their caregiver should be informed to be aware of these symptoms (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Lactose intolerance

Temaze contains lactose. Patients with rare hereditary problems such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Temaze.

Use in Hepatic Impairment

Patients with impaired hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have had elevations of

liver enzymes. As with other benzodiazepines, periodic 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.

Use in Renal Impairment

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable.

Use in the Elderly

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Elderly or debilitated patients

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Opioids

The concomitant use of temazepam with opioids increases the risk of sedation, respiratory depression, coma and death due to additive CNS depressant effect. The dosage and duration of concomitant use should be limited (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Concomitant use with Opioids).

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.

Potentiation of Anticholinergic Effects

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

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.

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.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Somnambulism and associated behaviour).

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

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.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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.

Distribution

Approximately 96% of unchanged drug is bound to plasma proteins.

Metabolism

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.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Bottles: The tablets contain lactose monohydrate, maize starch, microcrystalline cellulose and magnesium stearate.

Blisters: The tablets contain lactose monohydrate, maize starch, microcrystalline cellulose, magnesium stearate and Sunset Yellow FCF Aluminium Lake

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

Blisters: Store below 25°C. Store in original container. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

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.

Australian Register of Therapeutic Goods (ARTG)

AUST R 63863 – TEMAZE temazepam 10 mg tablet bottle

AUST R 408408 – TEMAZE temazepam 10 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

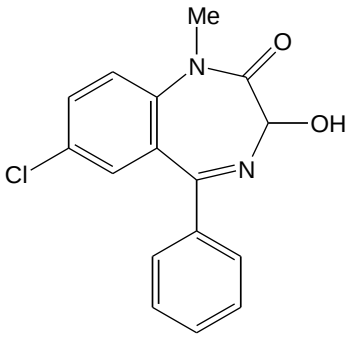
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

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

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.

CAS Number

846-50-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

13/05/1998

10 DATE OF REVISION

07/09/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Removed galactose from Excipients with known effect
3	Visual appearance update to reflect change in formulation for blisters

6.1	Update of list of Excipients to reflect change in formulation for blister packed product
6.4	Inclusion of storage conditions for blister packs
6.5	Insert AUST R numbers
8	Update sponsor's details

Temaze_pi\Sep23/00 (CCDS 10-Aug-2020)