

AUSTRALIAN PRODUCT INFORMATION

APO-ZOLPIDEM (ZOLPIDEM TARTRATE) TABLETS

WARNING: Zolpidem may be associated with potentially dangerous complex sleep-related behaviours which may include sleep walking, sleep driving and other bizarre behaviours. Zolpidem is not to be taken with alcohol. Caution is needed with other CNS depressant drugs. Limit use to four weeks maximum under close medical supervision.

1 NAME OF THE MEDICINE

Zolpidem tartrate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg or 10 mg of zolpidem tartrate as the active ingredient.

For the full list of excipients see section **6.1 List of excipients**.

3 PHARMACEUTICAL FORM

5 mg tablets

Pink, capsule-shaped, film-coated tablets, imprinted "APO" on one side and "ZOL 5" on the other side

10 mg tablets

White, modified oval, scored tablets, imprinted "APO" on one side and "1" European bisect "0" on the other side

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

APO-Zolpidem tablets are indicated for the short term treatment of insomnia in adults (see section **4.2 Dose and method of administration**).

4.2 DOSE AND METHOD OF ADMINISTRATION

APO-Zolpidem tablets are intended for oral administration

Zolpidem acts rapidly and should therefore be taken immediately before retiring. As with all hypnotics, long-term use is not recommended. Treatment should be as short as possible and should not exceed four weeks.

Discontinuation of Treatment: see section 4.8 Adverse effects (Undesirable effects).

Withdrawal Effects: see section 4.4 Special warnings and precautions for use.

Recommended Dosage

Adults

10 mg to be taken at night.

Elderly or Debilitated Patients

Since elderly or debilitated patients may be especially sensitive to the effects of zolpidem,

5 mg to be taken at night. This dose should not be exceeded.

Hepatic impairment

As clearance and metabolism of zolpidem is reduced in hepatic impairment, dosage of 5 mg to be taken at night is recommended, with particular caution being exercised in elderly patients.

In adults less than 65 years the dosage may be increased if the clinical response is inadequate and the drug is well tolerated.

Renal impairment

No dosage adjustment is necessary in these patients, although they should be closely monitored.

Children

The use of zolpidem in children under 18 years is contraindicated.

4.3 CONTRAINDICATIONS

- Obstructive sleep apnoea.
- Known hypersensitivity to zolpidem or other ingredients in the tablet.
- Myasthenia gravis.
- Severe hepatic insufficiency.
- Acute and/or severe pulmonary insufficiency.
- Prior or concomitant intake with alcohol.
- Zolpidem should not be prescribed for children under 18 years of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed.

The failure of insomnia to remit after a 7 to 14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder, and the patient should be carefully re-evaluated at regular intervals.

Withdrawal, Rebound, Dependence and Tolerance

Tolerance

Continuous long-term use of zolpidem is not recommended and should not exceed four weeks.

Some loss of efficacy to the hypnotic effects of sedative/ hypnotic agents may develop after repeated use for a few weeks.

Dependence

Use of zolpidem may lead to the development of abuse and/or physical and psychological dependence. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or alcohol or drug abuse. Zolpidem should be used with extreme caution in patients with current or a history of alcohol or drug abuse. These patients should be under careful surveillance when receiving hypnotics.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

Rebound Insomnia

A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur when the medicinal product is discontinued.

There are indications that, in the case of sedative/ hypnotic agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When zolpidem is used in accordance with the recommendations for dosage, duration of treatment and warnings, the risk of withdrawal symptoms or rebound phenomena occurring is minimal.

Severe injuries

Due to its pharmacological properties, zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries.

Patients with Long QT syndrome

An *in vitro* cardiac electrophysiological test showed that under experimental conditions, using very high concentration and pluripotent stem cells, zolpidem may reduce the hERG related potassium currents. As a precaution, the benefit/risk ratio of zolpidem treatment in patients with known congenital long QT syndrome should be carefully considered

CNS Effects

As with all patients taking CNS-depressant medications, patients receiving zolpidem should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from zolpidem therapy. Patients should be advised that their tolerance for other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of zolpidem. Prior or concomitant intake with alcohol is contraindicated (see section **4.3 Contraindications**).

Respiratory Function

Both animal and human pharmacology studies performed with zolpidem have not observed any effect on the respiratory centre. However, as other sedative/hypnotics have the capacity to depress respiratory drive, caution is advised when zolpidem is administered to patients with respiratory insufficiency (see section **4.3 Contraindications**).

Use in hepatic impairment

As clearance and metabolism of zolpidem is reduced in hepatic impairment, dosage should begin at 5 mg with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated (see sections **4.4 Special warnings and precautions for use - Use in the Elderly** and **4.2 Dose and method of administration**).

Use in renal impairment

Dosage reduction is not necessary in patients with renal impairment, however, as a general precaution, these patients should be monitored closely (see section **4.2 Dose and method of administration**).

Memory Impairment

Sedative/hypnotic agents may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours.

Suicidality, Depression, Psychosis and Schizophrenia

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including zolpidem.

Zolpidem should be administered with caution in patients exhibiting symptoms of depression. Zolpidem is not recommended as primary therapy in patients with psychotic illness, including depression and psychosis. In such conditions, psychiatric assessment and supervision are necessary as depression may increase in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Pre-existing depression may be unmasked during the use of zolpidem. Suicidal tendencies may be present or uncovered and protective measures may be required. Intentional overdose is more common in this group of patients, therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Other Psychiatric and Paradoxical Reactions

Other psychiatric and paradoxical reactions such as acute rage, restlessness, insomnia exacerbated, agitation, irritability, aggression, delusions, anger, nightmares, hallucinations, stimulation or excitement, abnormal behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zolpidem. Should such reactions occur, zolpidem should be discontinued. These reactions are more likely to occur in the elderly.

Somnambulism and Associated Behaviours

Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, making phone calls or having sex, with amnesia for the event, have been reported in patients who had taken zolpidem and were not fully awake. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of such behaviours, as does the use of zolpidem at doses exceeding the maximum recommended dose. Discontinuation of zolpidem should be strongly considered for patients who report such behaviours (for example, sleep driving) due to the risk to the patient and others (see sections **4.5 Interactions with other medicines and other forms of interactions** and **4.8 Adverse effects (Undesirable effects)**). These events can occur in sedative-hypnotic naive as well as sedative-hypnotic experienced patients.

Psychomotor Impairment

Zolpidem has CNS-depressant effects. The risk of psychomotor impairment, including impaired driving ability, is increased if a dose higher than the recommended dose is taken, or zolpidem is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zolpidem

Interactions with Alcohol

Prior or concomitant intake with alcohol is contraindicated (see section **4.3 Contraindications**). Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance (see section **4.4 Special warnings and precautions for use - 'Somnambulism and Associated Behaviours'**, above).

Risks from Concomitant use with Opioids

Concomitant use of sedative-hypnotic drugs, including zolpidem, with opioids may result in sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of opioids and zolpidem for use in patients for whom alternative treatment options are inadequate.

If a decision is made to prescribe zolpidem concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. (see section **4.5 Interactions with other medicines and other forms of interactions**).

Severe Anaphylactic and Anaphylactoid Reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

Epilepsy

Abrupt withdrawal of CNS-depressant drugs in persons with convulsive disorders has been associated with a temporary increase in the frequency and/or severity of seizures.

As with other sedative/hypnotics, caution is advised when zolpidem is used in these patients.

Abuse

Caution must be exercised in administering zolpidem 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.

Use in the Elderly or Debilitated Patient

Elderly and debilitated patients may be particularly sensitive to the effects of zolpidem, therefore a 5 mg dose is recommended. This dose should not be exceeded in these patients (see section **4.2 Dose and method of administration**).

Such patients may be particularly susceptible to the sedative effects of the medication and associated giddiness, ataxias and confusion, which may increase the possibility of a fall.

Paediatric use

The use of zolpidem in children under 18 years is contraindicated.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Central Nervous System Depressants

Coadministration of Zolpidem with other CNS depressants should be exercised with caution since the central depressant effect may be additive. CNS depressants include alcohol, benzodiazepines, barbiturates, sedative/hypnotics, antidepressant agents (including tricyclic antidepressants), MAOIs, antipsychotics, phenothiazines, skeletal muscle relaxants, antihistamines, neuroleptics, narcotic analgesics or anaesthetics.

In the case of narcotic analgesics enhancement of euphoria may also occur.

Opioids

The concomitant use of sedative-hypnotic drugs, including zolpidem, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of zolpidem and opioids (see section **4.4 Special warnings and precautions for use 'Risks from Concomitant use with Opioids'**).

Alcohol

Prior or concomitant intake with alcohol is contraindicated (see section **4.3 Contraindications**).

Patients should be advised that their tolerance for alcohol and other CNS depressants might be reduced and have an additive effect on psychomotor performance. The use of alcohol and other CNS depressants with zolpidem appears to increase the risk of somnambulism and associated behaviours (see section **4.4 Special warnings and precautions for use - Somnambulism and Associated Behaviours**).

Imipramine

The sedative effects of imipramine 75 mg and zolpidem 20 mg were shown to be additive when the two compounds were given concomitantly in healthy volunteers. No pharmacokinetic interaction was shown between zolpidem and imipramine or its metabolite, desipramine.

Chlorpromazine

The combination of zolpidem 10 mg and chlorpromazine 50 mg in healthy volunteers produced an addition of effects seen in psychometric tests and decreased alertness and psychomotor performance. No pharmacokinetic interaction was observed.

Haloperidol

No evidence of pharmacokinetic interaction between zolpidem 20 mg and haloperidol 2 mg was seen when they were given concurrently to healthy volunteers.

Caffeine

No change in the sleep inducing effect of zolpidem was seen when caffeine 300 mg was given in the evening 45 minutes before administration of zolpidem 20 mg to 8 healthy volunteers.

Warfarin

Prothrombin times were not prolonged in healthy adults when zolpidem 20 mg was administered for four consecutive nights concomitantly with warfarin. Warfarin had been given for at least ten days previously to produce a 1.5 times prolongation of baseline prothrombin time in the volunteers. Zolpidem does not appear to modify the anticoagulant activity of warfarin.

Digoxin

The concurrent administration of zolpidem 10 mg once daily and digoxin 0.25 mg in healthy volunteers did not show any alteration of the pharmacokinetic or pharmacodynamic profile of digoxin.

H2-antagonist

Simultaneous administration of zolpidem 20 mg and cimetidine 200 mg tds and 400 mg at night or ranitidine 150 mg bd did not cause any significant change in psychometric tests from those produced by zolpidem alone. No change in the pharmacokinetics of zolpidem was caused by concomitant administration of either cimetidine or ranitidine.

Hepatic Enzyme Inhibitors and Inducers

Zolpidem is metabolised via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2. Compounds which inhibit or enhance certain hepatic enzymes (particularly cytochrome P450) may increase or decrease the activity of some hypnotics like zolpidem. The pharmacodynamic effect of zolpidem is decreased when it is administered with rifampicin (a CYP3A4 inducer). Ketoconazole has a significant but only quantitatively modest reduction in zolpidem clearance, with an increase in its pharmacodynamic effects.

Patients should be advised that use of zolpidem with ketoconazole may enhance the sedative effects of zolpidem.

However, when zolpidem is administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category B3

This drug has been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is uncertain in humans. The use of zolpidem is not recommended during pregnancy

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines or other sedative-hypnotic drugs such as zolpidem during pregnancy.

Administration of zolpidem during the late phase of pregnancy or during labour has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties, and respiratory depression.

If zolpidem is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the product if she intends to become or suspects that she is pregnant.

Teratogenic Effects

In reproductive toxicity studies, rats treated with oral zolpidem with estimated exposures (AUC) to zolpidem and its major metabolite of 41 and 15 times, respectively, the anticipated clinical exposure did not exhibit teratogenic effects but post-implantation survival index and postpartum viability of the offspring were significantly reduced. In rats, delayed ossification of foetal skull bones occurred at zolpidem and metabolite exposure levels of 8 and 3 times, respectively, the anticipated clinical exposure.

Rabbits treated with oral zolpidem with estimated exposure to zolpidem of 0.6-2.6 times the anticipated clinical exposure did not exhibit teratogenic effects, but there was increased post-implantation loss.

Although animal studies have not shown any teratogenic effects with zolpidem, the safety of zolpidem in human pregnancy has not been established.

Non-Teratogenic Effects

Cases of severe neonatal respiratory depression have been reported when zolpidem was used with other CNS depressants at the end of pregnancy.

Infants born to mothers who took hypnotics chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

Use in lactation

The use of zolpidem in nursing women is not recommended as small quantities of zolpidem are excreted into breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

This preparation is to aid sleep. Patients should not drive or operate machinery for 8 hours after taking zolpidem.

Drowsiness may continue the following day. After ingesting the medicine, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor co-ordination such as operating machinery or driving a motor vehicle, including potential impairment of the performance of such activities that may occur the day following ingestion of zolpidem.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials Data

There is evidence of a dose-relationship for adverse effects associated with Zolpidem use, particularly for certain CNS events. These occur most frequently in elderly patients.

Associated with Discontinuation of Treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in US premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%) and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar European trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%) and nausea (0.6%).

Incidence in Controlled Clinical Trials

Most Commonly Observed Adverse Events in Controlled Trials

During short-term treatment (up to 10 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of Zolpidem and seen at statistically significant differences from placebo treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1 %) and diarrhoea (1 %). During longer-term treatment (28 to 35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo treated patients were dizziness (5%) and drugged feelings (3%).

Adverse Events Observed at an Incidence of $\geq 1\%$ in Controlled Trials

Tables 1 and 2 enumerate treatment emergent adverse event frequencies that were observed at an incidence equal to 1 % or greater among patients with insomnia who received zolpidem in US placebo controlled trials. Events reported by investigators were classified utilising a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event frequencies.

Table 1 was derived from a pool of 11 placebo-controlled short-term US efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

Table 1**Incidence of Treatment Emergent Adverse Experiences in Short-Term Placebo Controlled Clinical Trials (Percentage of Patients Reporting)**

BODY SYSTEM / ADVERSE EVENT *	ZOLPIDEM (< 10 mg) (n = 685)	PLACEBO (n = 473)
Central & Peripheral Nervous System		
Headache	7	6
Drowsiness	2	/
Dizziness	1	/
Gastrointestinal System		
Nausea	2	3
Diarrhoea	1	/
Musculoskeletal system		
Myalgia	1	2

* Events reported by at least 1 % of zolpidem patients are included

Table 2 was derived from a pool of three placebo controlled long-term efficacy trials involving zolpidem (zolpidem tartrate). These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10 or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1 % for zolpidem patients.

Table 2**Incidence of Treatment Emergent Adverse Experiences in Long-Term Placebo Controlled Clinical Trials (Percentage of Patients Reporting)**

BODY SYSTEM / ADVERSE EVENT *	ZOLPIDEM (< 10 mg) (n = 152)	PLACEBO (n = 161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	/
Chest pain	1	/
Fatigue	1	2
Cardiovascular System		
Palpitation	2	/
Central & Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	/
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	/
Amnesia	1	/
Anxiety	1	1
Nervousness	1	3
Sleep	1	/

BODY SYSTEM / ADVERSE EVENT *	ZOLPIDEM (< 10 mg) (n = 152)	PLACEBO (n = 161)
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhoea	3	2
Abnormal pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immune System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory system		
Upper respiratory infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin & Appendages		
Rash	2	1
Urogenital System		
Urinary tract infection	2	2

* Events reported by at least 1 % of patients treated with zolpidem.

Post-Marketing Data

Gastrointestinal disorders

Common: Diarrhoea, nausea, vomiting, abdominal pain.

Nervous system disorders

Common: Dizziness, somnolence, headache, exacerbated insomnia, cognitive disorders such as anterograde amnesia (amnestic effects may be associated with inappropriate behaviour).

Uncommon: Paraesthesia, tremor, disturbance in attention, speech disorder

Rare: Ataxia, dysarthria, depressed level of consciousness.

Eye disorders

Uncommon: Diplopia, vision blurred, visual impairment

Psychiatric Disorders

Common: Drowsiness, hallucinations, agitation, nightmare, depression.

Uncommon: Confusion, memory disturbances, reduced alertness, irritability, restlessness, aggressiveness, somnambulism, (see section **4.4 Special warnings and precautions for use – ‘Somnambulism and Associated Behaviours’**), euphoric mood.

Rare: Perceptual disturbances, , aggravated insomnia, libido disorder, delusion, rages, inappropriate behaviour, dependence (withdrawal symptoms, or rebound effects may occur after treatment discontinuation), other adverse behavioural effects. Anger and abnormal behaviour have been reported.

Immune system disorders

Rare: Angioneurotic oedema.

Metabolism and nutritional disorders

Uncommon Appetite disorder

Respiratory, thoracic and mediastinal disorders

Very rare: Respiratory depression

Skin and subcutaneous tissue disorders

Uncommon: Hyperhidrosis, rash, pruritus, urticaria.

Musculoskeletal and connective tissue disorders

Common: Back pain

Uncommon: Arthralgia, myalgia, muscle spasms, neck pain, muscular weakness

Hepatobiliary disorders

Uncommon: Elevated liver enzymes

Rare: Hepatocellular, cholestatic and mixed liver injury

Infections and infestations

Common: Upper respiratory tract infection, lower respiratory tract infection

General disorders and administration site conditions

Common: Fatigue.

Rare: Fall, ataxia/gait disturbances, drug tolerance.

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 <http://www.tga.gov.au/reporting-problems> and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Symptoms

In reports of overdose with zolpidem alone, or with other CNS depressant agents (including alcohol), impairment of consciousness has ranged from somnolence to light coma. Fatalities have occurred when overdoses of multiple CNS depressants were taken.

Treatment

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Sedative drugs should be withheld, even if excitation occurs. Zolpidem has been shown in trials to be non-dialysable.

Use of flumazenil may be considered when serious symptoms are observed. However, flumazenil administration may contribute to the appearance of neurological symptoms, such as convulsions, since zolpidem does not exhibit the anticonvulsant effects of benzodiazepines.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem selectively binds the omega-1 receptor subtype (also known as the benzodiazepine-1 subtype) which is the alpha unit of the GABA-A receptor complex.

Whereas benzodiazepines non-selectively bind all three omega receptor subtypes, zolpidem preferentially binds the omega-1 subtype. The modulation of the chloride anion channel via this receptor leads to the specific sedative effects demonstrated by zolpidem, i.e. the preservation of deep sleep (stages 3 and 4 slow wave sleep).

These effects are reversed by the benzodiazepine antagonist flumazenil.

In animals, the selective binding of zolpidem to omega-1 receptors may explain the virtual absence at hypnotic doses of myorelaxant and anticonvulsant effects in animals which are normally exhibited by benzodiazepines which are not selective for omega-1 sites.

In humans the preservation of deep sleep (stages 3 and 4 slow wave sleep) may be explained by the selective omega-1 binding by zolpidem. All identified effects of zolpidem are reversed by the benzodiazepine antagonist flumazenil.

Clinical trials

Insomnia in Non-Elderly Adults

Short-term (1 to 2 nights) placebo controlled studies in 620 volunteers showed that zolpidem 2.5 to 10 mg decreased the latency of persistent sleep in a dose dependent manner. No further increase in efficacy was seen in doses up to zolpidem 40 mg.

The efficacy of zolpidem 2.5 to 20 mg was investigated in 11 placebo controlled studies in 1,606 (513 received zolpidem 10 mg) non-elderly insomniacs over a period of 2 to 35 nights. Zolpidem 10 mg was superior to placebo using both objective (polysomnography) and subjective methods of assessment. Zolpidem 20 mg showed little increase in efficacy.

Insomnia in the Elderly

Four studies in 145 elderly (> 65 years) patients showed, using objective (2 studies) and subjective (4 studies) methods of assessment, that zolpidem 5 mg was the dose giving the optimum efficacy/ safety ratio.

Next Day Residual Effects

There was no evidence of residual next day effects seen with zolpidem in several studies utilising the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study.

Rebound Effects

Although there were no studies to exclude this effect, there was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of zolpidem. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory Impairment

Two small studies (n = 6 and n = 9) using objective measures of memory yielded little evidence for memory impairment following the administration of zolpidem. There was subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of zolpidem, predominantly at doses above 10 mg.

Effects on Sleep Stages

In studies that measured the percentage of sleep time spent in each sleep stage, zolpidem has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

The hypnotic efficacy and safety of Zolpidem has not been assessed in children and pregnant women.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Zolpidem has both a rapid absorption and onset of hypnotic action.

Peak plasma concentration is reached at between 0.5 and 3 hours.

Following oral administration, bioavailability is 70% due to a moderate first-pass metabolism.

Zolpidem pharmacokinetic profile is linear in the therapeutic dose range, and is not modified upon repeated administration.

A food effect study in 30 healthy male volunteers compared the pharmacokinetics of zolpidem 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 15 and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hours). The half-life remained unchanged. These results suggest that, for faster sleep onset, zolpidem tablets should not be administered with or immediately after a meal.

Distribution

Protein binding amounts to approximately 90%. The distribution volume in adults is 0.54 ± 0.02 L/kg and decreases to 0.34 ± 0.05 L/kg in the very elderly.

Metabolism

The main cytochrome P450 enzyme involved in the hepatic biotransformation of zolpidem is CYP3A4. CYP1A2 and CYP2D6 contribute minimally to the metabolism of zolpidem (see section **4.5 Interactions with other medicines and other forms of interactions**).

Excretion

All metabolites are pharmacologically inactive and are eliminated in the urine (56%) and in the faeces (37%). Furthermore, they do not interfere with zolpidem plasma binding.

The elimination half-life is short, with a mean value of 2.4 hours (+/- 0.2 h) and a duration of action of up to 6 hours.

Special populations

Zolpidem did not accumulate in young adults following nightly dosing with zolpidem tartrate 20 mg tablets for two weeks.

In the elderly, the recommended dose for zolpidem is 5 mg (see sections **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**). This recommendation is based on several studies in which the mean C_{max} , $T_{1/2}$ and AUC were significantly increased when compared to results in young adults.

Zolpidem did not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of zolpidem in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single oral zolpidem 20 mg dose, mean C_{max} and AUC were found to be two times (250 versus 499 ng/mL) and five times (788 versus 4,203 ng.hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hours (range 4.1 to 25.8 hours) was greater than that observed in normals of 2.2 hours (range 1.6 to 2.4 hours). Dosing should be modified accordingly in patients with hepatic insufficiency (see sections **4.4 Special warnings and precautions for use** and **4.2 Dose and method of administration**).

In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected. Zolpidem has been shown to be non-dialysable.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Zolpidem was not genotoxic in assays for gene mutations (*Salmonella typhimurium* histidine reversion assay, L5178Y mouse lymphoma assay), for chromosomal aberrations (human lymphocytes, mouse micronucleus assay) and for DNA repair assays (in human fibroblasts and rat hepatocytes). The mutagenic activity of zolpidem and/or its metabolites was equivocal in a Chinese hamster V79/HRPT gene mutation assay in the presence of metabolic activation.

Carcinogenicity

Two year dietary carcinogenicity studies on zolpidem were conducted in rats and mice. No evidence of carcinogenic potential was observed in mice at plasma concentrations (AUC) of zolpidem and its major human metabolite of about 2 and 7-12 times, respectively, the anticipated clinical exposure at the maximum recommended clinical dose. An increased incidence of renal liposarcomas was observed in male rats (6% cf. 0 in controls) at plasma

concentrations (AUC) of zolpidem and its major metabolite of at least 22 and 9 times, respectively, the anticipated human exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Microcrystalline cellulose
- sodium starch glycollate
- magnesium stearate
- hypromellose
- hyprolose
- macrogol 8000
- iron oxide red (5 mg only)
- titanium dioxide

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

Store below 30°C. Store in original package.

6.5 NATURE AND CONTENTS OF CONTAINER

APO-Zolpidem 5 mg tablets

Blister Pack (Aluminium silver foil) of 7 or 14 tablets (AUST R 127151)

Bottle (white, round HDPE bottle with blue PP child-resistant cap) of 7 or 14 tablets (AUST R 127167)

APO-Zolpidem 10 mg tablets

Blister Pack (Aluminium silver foil) of 7 or 14 tablets (AUST R 127174)

Bottle (white, round HDPE bottle with blue PP child-resistant cap) of 7 or 14 tablets (AUST R 127178)

Not all strengths, pack types and/or pack sizes may be available.

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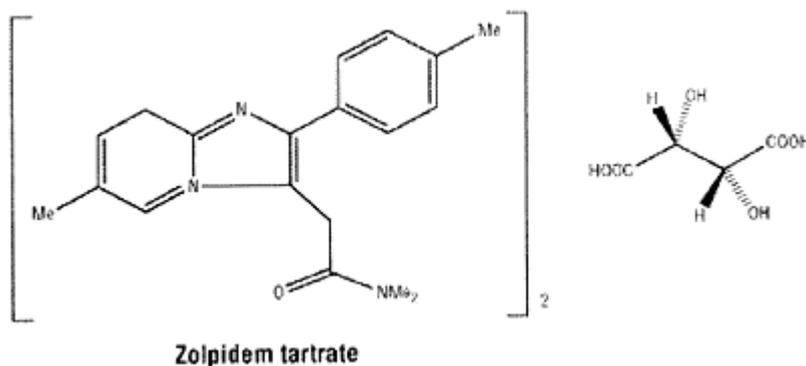
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Zolpidem tartrate is a white to off white colourless, crystalline powder, slightly soluble in water.

Chemical structure



Chemical Name: (bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate).

Molecular Formula: $C_{42}H_{48}N_6O_8$

Molecular Weight: 764.9

CAS number 99294-93-6 (zolpidem tartrate)

82626-48-0 (zolpidem)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11 July 2007

10 DATE OF REVISION

6 June 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
4.2, 4.4, 4.5, 4.6, 4.8	Safety related updates