AUSTRALIAN PI – APO- ZOPICLONE TABLETS (ZOPICLONE)

1 NAME OF THE MEDICINE

Zopiclone

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Zopiclone is a fine white or slightly cream crystalline powder with a melting point of 176-178°C. Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in acetone, practically insoluble in ethanol (96 per cent). It dissolves in dilute mineral acids.

The tablets are white to off white oval film coated tablets with breakline on one side and plain on the other side. Each tablet contains 7.5 mg of the active ingredient. In addition each tablet contains calcium hydrogen phosphate dihydrate, lactose monohydrate, sodium starch glycollate type A, povidone, maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose, macrogol 6000, titanium dioxide, and purified talc.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short term treatment of insomnia (2 to 4 weeks).

4.2 DOSE AND METHOD OF ADMINISTRATION

Use in Adults

7.5 mg by oral administration shortly before retiring for a maximum of 2-4 weeks. This dose should not be exceeded. Depending on clinical response, the dose may be lowered to 3.75 mg. Zopiclone is not recommended for long term use (i.e. periods of more than 4 weeks). If used for long periods, treatment should be withdrawn gradually. (See '4.4 Special warnings and precautions for use')

Use in the Elderly

In the elderly and/or debilitated patient an initial dose of 3.75 mg is recommended. The dose may be increased to a maximum of 7.5 mg if the starting dose does not offer adequate therapeutic effect, but in clinical trials, 25% of elderly patients treated with zopiclone experienced CNS side-effects at the higher dose. Zopiclone should be used with caution in these patients. (See also '4.4 Special warnings and precautions for use').

Use in Children

Zopiclone is contraindicated in children. Dosage has not been established.

Use in Patients with Renal Impairment

In patients with renal insufficiency: although no accumulation of zopiclone or of its metabolites has been detected in cases of renal insufficiency, it is recommended that patients with impaired renal function should start treatment with 3.75 mg.

Use in Patients with Hepatic Impairment

The recommended dose is 3.75 mg depending on acceptability and efficacy. Up to 7.5 mg may be used with caution in appropriate cases.

Alternative Therapy

For long term treatment of insomnia, alternative non-pharmacological methods should be considered. Effective practical management of insomnia must respond to the presenting characteristics of the complaint. Giving accurate information is a form of treatment; there is benefit in discussing some simple facts with the patient and relating them to the problem, thereby assisting the patient to place the sleep problem in its context. Sleep hygiene such as reduction of caffeine intake, should be exercised. Programmes designed to establish an optimal sleeping pattern for the patient may also be useful as are relaxation techniques designed to assist the patient deal with tension and intrusive thoughts in bed.

4.3 CONTRAINDICATIONS

- Patients with known hypersensitivity to zopiclone or any of the excipients.
- Prior or concomitant use of alcohol.
- Myasthenia gravis.
- Severe impairments of respiratory function.
- Acute cerebrovascular accident.
- Sleep apnoea syndrome.
- Severe hepatic insufficiency.
- Zopiclone in contraindicated in children

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Prolonged use of hypnotics is not recommended especially in the elderly.

Dependence

Zopiclone should be prescribed for short periods only (2-4 weeks). Continuous long term use is not recommended. Use of sedative-hypnotic agents like zopiclone may lead to the development of physical and psychological dependence or abuse. It is therefore recommended that after prolonged use the dose should be decreased gradually and the patient advised about such a possibility (see ‘4.8 Adverse effects (Undesirable effects)’).

Risks of dependence or abuse increase with:

- Dose and duration of treatment.
- History of alcohol and/or drug abuse.
- Use with alcohol or other psychotropics.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

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. Since the risk of such phenomena is greater after abrupt discontinuation of zopiclone, especially after prolonged treatment, it is, therefore, recommended to decrease the dosage gradually and to advise the patient accordingly (see ‘4.8 Adverse effects (Undesirable effects)’).

Amnesia

Anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after the intake of the tablet. To reduce the possibility of anterograde amnesia, patients should ensure that:

- they take the tablet strictly when retiring for the night,
- they are able to have a full night sleep.

Other Psychiatric and Paradoxical Reactions

Other psychiatric and paradoxical reactions have been reported (see '4.8 Adverse effects (Undesirable effects)'), like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, inappropriate behaviour and other adverse behavioural effects are known to occur when using sedative/hypnotic agents like zopiclone. Should this occur, use of zopiclone 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, or making phone calls, with amnesia for the event, have been reported in patients who have taken zopiclone and were not fully awake. The use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose. Discontinuation of zopiclone would be strongly considered for patients who report such behaviours (see '4.5 Interactions with other medicines and other forms of interactions, Alcohol' and '4.8 Adverse effects (Undesirable effects)').

Depression, Psychosis and Schizophrenia

As with other hypnotics, zopiclone does not constitute a treatment of depression and may even mask its symptoms. Caution should be exercised if zopiclone is prescribed to depressed patients, including those with latent depression, particularly when suicidal tendencies may be present and protective measures may be required.

Epilepsy

Patients with a history of seizures should not be abruptly withdrawn from any CNS depressant drug, including zopiclone.

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 zopiclone. 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 zopiclone should not be rechallenged with the drug.

Respiratory Insufficiency

Caution should be exercised in treating patients with chronic respiratory insufficiency. Treatment should be initiated on a dose of 3.75mg and if necessary, should be carried out at 7.5mg.

Hormonal Systems

Treatment of rats with zopiclone increases hepatic thyroid hormone metabolism of T4, resulting in increases in thyroid stimulating hormone (TSH) and T3 levels, and decreases in T4 levels. It is suggested that zopiclone not be administered to individuals with impaired thyroid hormone homeostatic mechanisms or with conditions linked to hormonal imbalances.

Abuse

Caution must be exercised in administering zopiclone to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative.

Use in hepatic impairment

In patients with severe hepatic insufficiency (serum albumin less than 30 g/l or presence of gross oedema), the elimination of zopiclone may be significantly reduced. Treatment should be initiated on a dose of 3.75mg and if necessary, may be increased to 7.5mg.

Use in renal impairment

Zopiclone is removed by dialysis.

Use in the elderly or debilitated patients

Such patients may be particularly susceptible to the sedative effects of zopiclone and associated giddiness, ataxia and confusion, which may increase the possibility of a fall. (See '4.2 Dose and method of administration').

Paediatric use

The safe and effective dose of zopiclone in children and adolescents under 18 years of age has not been established (see '4.3 Contraindications').

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Alcohol

Concomitant intake with alcohol is not recommended. The sedative effect of zopiclone may be enhanced when the product is used in combination with alcohol.

CNS Depressants

Additive CNS depressant effects should be expected if zopiclone is administered concomitantly with other medications which themselves produce CNS depression, for example, barbiturates, benzodiazepines, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics, anaesthetics, neuroleptics, anxiolytics, antiepileptics (see '4.4 Special warnings and precautions for use'). In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence.

Other

Erythromycin has been reported to increase significantly zopiclone concentrations at 0.5 and 1 hour after ingestion of zopiclone. The total AUC of zopiclone increased by 80% in 10 healthy volunteers. Accelerated absorption of zopiclone in the presence of erythromycin may lead to faster hypnotic effects.

Plasma levels of zopiclone may be increased when co-administered with CYP3A4 inducers, such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir.

Plasma levels of zopiclone may be decreased when co-administered with CYP3A4 inducers, such as rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Zopiclone has been shown to severely reduce fertility in male rats treated with 50 mg/kg/day or greater. The significance of this finding for humans is not known.

Use in Pregnancy (Category C)

Insufficient data are available on zopiclone to assess its safety during human pregnancy and lactation, therefore the use of zopiclone during pregnancy is not recommended. Studies in animals have not shown evidence of an increased occurrence of foetal damage. However, zopiclone has been shown to cross the placenta, and increase postnatal mortality in rats given 10 mg/kg/day and above. Although the significance of this for humans is not known, it is likely that zopiclone may be harmful to the neonate

Treatment should be as short as possible and should not exceed four weeks including the period of tapering off. Moreover, infants born to mothers who took sedative/hypnotics agents 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.

If zopiclone is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuation of the product if she intends to become or suspects she is pregnant.

Moreover, if zopiclone is used during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia and respiratory depression can be expected.

Use in lactation

Zopiclone and/or its metabolites are excreted in breast milk so therefore use in nursing mothers is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with all patients taking CNS depressant medications, patients receiving zopiclone should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy after zopiclone therapy. Abilities may be impaired on the day following use. It has been reported that the risk that zopiclone adversely affects driving ability is increased by concomitant intake of alcohol. Therefore, driving is not recommended after the concomitant intake of zopiclone and alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The side-effects most commonly seen in clinical trials is taste alteration (bitter taste).

More Common Reactions

Gastrointestinal: bitter taste, dry mouth

Nervous System: drowsiness, headaches, fatigue

Less Common Reactions

Gastrointestinal: heartburn, constipation, diarrhoea, nausea, coated tongue, bad breath, anorexia or increased appetite, vomiting, epigastric pains, dyspepsia.

Cardiovascular: palpitations in elderly patients. Skin: urticaria, tingling.

Reproductive: impotence, ejaculation failure, libido disorder.

Nervous system: agitation, anxiety, loss of memory including retrograde amnesia, anterograde amnesia, confusion, dizziness, weakness, somnolence, asthenia, feeling of drunkenness, euphoria, depression, co-ordination abnormality, hypotonia, speech disorder, hallucinations (auditory and visual), behavioural disorders, aggression, tremor, rebound insomnia, nightmares, irritability, inappropriate behaviour possibly associated with amnesia, sleep walking (see '4.4 Special warnings and precautions for use – Somnambulism and associated behaviours'), restlessness, delusion, anger, dependence, ataxia.

Withdrawal syndrome has been reported upon discontinuation (see '4.4 Special warnings and precautions for use'). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, 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. In very rare cases, seizures may occur.

Allergic or cutaneous: pruritus, rash. Angioedema and/or anaphylactic reactions have been reported very rarely.

Miscellaneous: blurred vision, micturition, mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely. Falls, predominantly in elderly patients, diplopia and muscular weakness have been reported.

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.

4.9 OVERDOSE

Overdose of zopiclone can be manifested by varying degrees of CNS depression ranging from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion and lethargy. In more severe cases, symptoms may include ataxia, hypotonia, hypotension, methaemoglobinaemia, respiratory depression and coma. Overdosage could be life threatening when combined with other CNS depressants, including alcohol. Other risk factors, such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome.

Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Activated charcoal is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be useful as an antidote. As 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 Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Zopiclone, a cyclopyrrolone derivative, is a short-acting hypnotic agent. Zopiclone belongs to a novel chemical class which is structurally unrelated to existing hypnotics. The pharmacological profile of zopiclone is similar to that of the benzodiazepines.

Pharmacological Actions

In sleep laboratory studies of 1 to 21-day duration in man, zopiclone reduced sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. Zopiclone delayed the onset of REM sleep but did not reduce consistently the total duration of REM periods. The duration of stage 1 sleep was shortened, and the time spent in stage 2 sleep increased. In most studies, stage 3 and 4 sleep tended to be increased, but no change and actual decreases have also been observed. The effect of zopiclone on stage 3 and 4 sleep differs from that of the benzodiazepines which suppress slow wave sleep. The clinical significance of this finding is not known.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Zopiclone is rapidly absorbed and distributed after oral administration, the time of maximum observed plasma concentration being about 1.75 hours.

Distribution

A study of 16 healthy volunteers receiving a single dose of 7.5 mg of zopiclone intravenously demonstrated the apparent volume of distribution of zopiclone to be 104 ± 15.5L. Autoradiographic studies in the rat showed rapid distribution into the blood and peak tissue levels at 0.5 hours in the liver, small intestines, stomach, kidneys and the adrenals. After twenty four hours the total residual radioactivity in the body of the rat was 8%.

The bioavailability of the 7.5 mg tablets in man is 76.3 ± 9.6%, a hepatic first pass effect has been demonstrated. In fresh human plasma, zopiclone is approximately 45% protein bound in the 25 - 100 ng/mL concentration range.

Metabolism

Zopiclone is extensively and rapidly metabolised by the liver. A large number of metabolites have been isolated and characterised, with the two major ones being the N-oxide, produced by oxidation of the piperazine nitrogen and the N-desmethyl produced by oxidative demethylation of the N-methyl piperazine. Only the N-oxide analogue has weak pharmacological activity.

Excretion

Zopiclone is rapidly eliminated, mainly by means of hepatic metabolism. The elimination half-life after a single oral dose is 5.26 ± 0.76 hours. The elimination half-life for the N-oxide metabolite is 4.44 ± 0.66 hours and that for the N-desmethyl metabolite is 7.28 ± 0.49 hours.

Renal clearance is 13.9 ± 7.0 mL/min which further shows that the major elimination pathway is by hepatic metabolism.

The amount of renal excretion is also low; unchanged zopiclone 3.6%, the N-oxide metabolites 11.4% and the N-desmethyl metabolite 13.4%.

Pharmacokinetics in Special Patient Groups

Elderly

In elderly patients, the absolute bioavailability is increased (94% vs 77% in young subjects), and the elimination half-life prolonged (approximately 7 hours).

Renal Impairment

In patients with mild to moderate renal insufficiency, the pharmacokinetics of zopiclone are not altered. Haemodialysis does not appear to increase the plasma clearance of the drug.

Hepatic Impairment

In patients with hepatic insufficiency, elimination half-life is prolonged (11.9) and time to peak plasma levels delayed (3.5 hours).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies, using a standard battery of tests, showed no evidence of gene mutations or chromosomal damage.

Carcinogenicity

Treatment with zopiclone by dietary administration for 2 years increased the incidence of thyroid carcinomas in male rats dosed with 100 mg/kg/day, and increased the incidence of mammary carcinoma in female rats dosed with 100 mg/kg/day, probably due to interference with thyroid hormone and 17β-estradiol metabolism. Studies with mice treated with zopiclone at dietary doses up to 100 mg/kg/day showed no evidence of drug-related carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section 2 and 3 – Qualitative and quantitative composition and pharmaceutical form.

6.2 INCOMPATIBILITIES

See Section 4.5-Interactions with other medicines and other forms of interactions.

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 25°C and Protect from Light.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister packs (Opaque PVDC coated PVC/Aluminium) of 30 tablets (AUST R 213071)

Not all pack sizes may be available

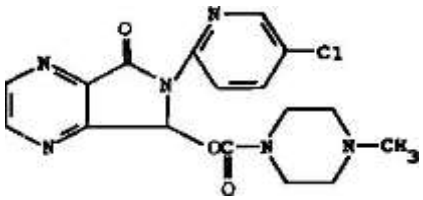
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Structural Formula:



Chemical Name:	(5*RS*)-6-(5-Chloropyridin-2-yl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-yl 4-methylpiperazine-1-carboxylate.
Molecular Formula:	$C_{17}H_{17}ClN_6O_3$
Molecular Weight:	388.8

CAS number

43200-80-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

4 September 2014

10 DATE OF REVISION

19 February 2018

Summary table of changes

Section Changed	Summary of new information
All	reformat
2 and 3	Update of ingredient names in accordance with the TGA's International Harmonisation of Ingredient Names (IHIN) project.