AUSTRALIAN PRODUCT INFORMATION – IMOVANE (ZOPICLONE) FILM COATED TABLET

1 NAME OF THE MEDICINE

Zopiclone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Imovane tablets contain 7.5 mg of the active ingredient zopiclone.

Zopiclone is a fine white or slightly cream crystalline powder with a melting point of 176-178°C. It is practically insoluble in acetone, soluble in dimethyl formamide and 0.1N hydrochloric acid and freely soluble in chloroform and dichloromethane.

The tablets also contain lactose monohydrate, calcium hydrogen phosphate dihydrate, wheat starch (gluten), sodium starch glycollate, magnesium stearate, hypromellose, macrogol 6000 and titanium dioxide.

3 PHARMACEUTICAL FORM

The tablets are scored white or almost white, elliptical, biconvex, film coated tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short term treatment of insomnia (7 – 14 days).

4.2 DOSE AND METHOD OF ADMINISTRATION

For oral use only. Use the lowest effective dose for short term treatment (7-14 days). Extension beyond the maximum treatment period should not take place without re-evaluation of the patient's status, since the risk of abuse and dependence increases with the duration of treatment.

Imovane should be taken in a single intake and not be readministered during the same night.

Adults

7.5 mg by oral administration shortly before retiring. This dose should not be exceeded. Depending on clinical response, the dose may be lowered to 3.75 mg.

Zopiclone is for short term treatment (7-14 days). ***See Section 4.4 Special warnings and precautions for use – Dependence*** for advice of gradual dose decrease after prolonged use.

Elderly Patients

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 Section 4.4 Special warnings and precautions for use).

Paediatric

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

Hepatic Insufficiency

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.

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.

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. Programs 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.

Patients who have previously experienced complex sleep behaviours after taking zopiclone.

Zopiclone is contraindicated in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Dependence

Zopiclone should be prescribed for short periods only (7-14 days). Continuous long term use is not recommended. Use of zopiclone may lead to the development of abuse and/or physical and psychological dependence. It is therefore recommended that after prolonged use the dose should be decreased gradually and the patient advised about such a possibility (see Section 4.8 Adverse effects (Undesirable effects)).

The risk of dependence or abuse increases with dose and duration of treatment. Cases of dependence have been reported more frequently in patients treated with zopiclone for longer than 4 weeks. The risk of abuse or dependence is also increased in patients with a history of psychiatric disorders and/or alcohol or drug abuse. The risk of dependence or abuse increases with the use of alcohol or other psychotropics. Zopiclone should be used with extreme caution in patients with current or a history of alcohol or drug abuse.

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 Section 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; and
- they are able to have a full night sleep.

Other Psychiatric and Paradoxical Reactions

Other psychiatric and paradoxical reactions have been reported (see Section 4.8 Adverse effects (Undesirable effects)), like restlessness, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, abnormal behaviour, delirium 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

Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake, may occur following the first or any subsequent use of zopiclone. Patients can be seriously injured or injure others during complex sleep behaviors.

Such injuries may be fatal. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex, with amnesia for the event) have also been reported. Patients usually do not remember these events. Postmarketing reports have shown that complex sleep behaviors may occur with zopiclone alone at recommended doses, with or without the concomitant use of alcohol or other central nervous system (CNS) depressants (See Section 4.5 Interactions with other medicines and other forms of interactions). Discontinue Imovane immediately if a patient experiences a complex sleep behavior. (See Section 4.3 Contraindications).

Depression, Suicidality, Psychosis and Schizophrenia

As with other hypnotics, zopiclone does not constitute a treatment of depression and may even mask its symptoms.

As with other sedative/hypnotic drugs, zopiclone should be administered with caution in patients exhibiting symptoms of depression, including those with latent depression. Suicidal tendencies may be present and protective measures may be required. Therefore the lowest possible quantity of zopiclone should be supplied to these patients to reduce the risk of intentional overdosage by the patient.

Pre-existing depression may be unmasked during use of zopiclone.

Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

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 zopiclone.

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.

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.

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.

As hypnotics have the capacity to depress respiratory drive, precautions should be observed if zopiclone is prescribed to patients with compromised respiratory function.

Hormonal Systems

Treatment of rats with zopiclone increases hepatic thyroid hormone metabolism of T4, resulting in increases in 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.

Risks from Concomitant Use with Opioids

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

If a decision is made to prescribe zopiclone 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).

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.

Chemical submission (Drug facilitated illicit use for criminal intent)

The rapid onset of sedation, coupled with the amnestic features of Imovane, particularly when combined with alcohol, administered without knowledge of the victim, has proven to induce incapacitation and thus facilitate criminal actions (which could be dangerous).

Healthcare Providers should prescribe Imovane according to their clinical evaluation and only in case of medical need as it may be used illicitly for chemical submission.

Haemolysis

Haemolysis/haemolytic anaemia have been reported in cases of Imovane overdose (see Section 4.9 Overdose).

Use in elderly

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 Section 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 Section 4.3 Contraindications).

Effects on laboratory tests

No data available

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 and other antidepressants, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics, anaesthetics, neuroleptics, hypnotics, anxiolytics, antiepileptics (see Section 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.

CYP450 inhibitors and inducers

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 which indicates that erythromycin can inhibit the metabolism of drugs metabolised by CYP 3A4. Accelerated absorption of zopiclone in the presence of erythromycin may lead to enhanced hypnotic effects.

Plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors 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 (phenobarbitone), phenytoin, and St. John's wort.

Opioids

The concomitant use of benzodiazepines and other sedative-hypnotic drugs, including zopiclone, 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 zopiclone and opioids (see Section 4.4 Special warnings and precautions for use).

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

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/d and above. Although the significance of this for humans is not known, it is likely that zopiclone may be harmful to the neonate.

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

Administration of zopiclone during the last three months of pregnancy or during labour, has been associated with effects on the neonate, such as hypothermia, hypotonia, feeding difficulties and respiratory depression, due to the pharmacological action of the product,

Zopiclone is for short term treatment of insomnia (7-14 days). 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. Appropriate monitoring of the newborn in the postnatal period is recommended.

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.

Use in lactation

Zopiclone and/or its metabolites are excreted in breast milk so therefore should not be used in nursing mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Zopiclone can impair daytime function in some patients even when taken as instructed. Some patients may still have zopiclone blood levels in the morning on the day following use that are high enough to produce impairment. Patients should be warned that impairment can occur despite feeling fully awake, in the absence of symptoms, or even with subjective improvement.

Zopiclone is not to be taken with alcohol or other sedative hypnotics (including other zopiclone products). If concomitant use of another CNS depressant or a drug that increases zopiclone blood levels is clinically warranted, dosage adjustments of zopiclone may be necessary.

The risk of psychomotor impairment, including impaired driving ability, is increased if:

- zopiclone is taken within 12 hours of performing activities that require mental alertness;
- zopiclone is taken with less than a full night sleep remaining;
- a higher dose than recommended is taken; or
- zopiclone is co-administered with other CNS depressants, alcohol, or with other drugs that increase the blood levels of zopiclone.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor

vehicle following administration of zopiclone and in particular during the 12 hours following that administration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

More Common Reactions

Nervous System disorders: drowsiness, headaches, fatigue.

Gastrointestinal disorders: bitter taste, dry mouth.

Less Common Reactions

Immune system disorders: Angioedema and/or anaphylactic reactions have been reported very rarely.

Nervous system disorders: 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, abnormal and/or inappropriate behaviour possibly associated with amnesia, complex sleep behaviours, including sleep walking (see Section 4.4 Special warnings and precautions for use – Somnambulism and associated behaviours'), restlessness, delirium, delusion, anger, dependence, ataxia, paresthesia, cognitive disorders such as memory impairment, disturbance in attention, speech disorder.

Withdrawal syndrome has been reported upon discontinuation (see Section 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.

Eye disorders: blurred vision and diplopia.

Cardiac disorders: palpitations in elderly patients.

Respiratory, Thoracic and Mediastinal disorders: dyspnea and respiratory depression have been reported.

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

Hepatobiliary disorders: mild to moderate increases in serum transaminases and/or alkaline phosphatase have been reported very rarely.

Skin and subcutaneous tissue disorders: pruritus, rash, urticaria and tingling have been rarely reported.

Musculoskeletal and connective tissue disorders: muscular weakness.

Renal and urinary disorders: micturition.

Reproductive system and breast disorders: impotence, ejaculation failure, libido disorder.

Injury, poisoning and procedural complications: falls, predominantly in elderly patients.

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

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, haemolysis/haemolytic anaemia, 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.

Treatment

Symptomatic and supportive treatment in an adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Activated charcoal may reduce absorption of the medicine 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. 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 Poisons Information Centre, telephone number 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Benzodiazepine related drugs, ATC code: N05C F01

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.
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%.

Elderly

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

Hepatic Insufficiency

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

Renal Insufficiency

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.

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 – Qualitative and quantitative composition

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 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

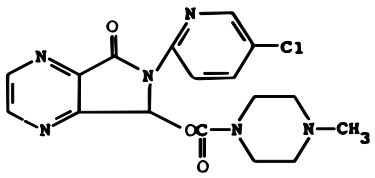
Imovane tablets containing 7.5 mg of zopiclone and are available in packs of 14 tablets.

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



The chemical name for zopiclone is 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b] pyrazin-5-yl 4-methylpiperazine-1-carboxylate.

Molecular Formula : $C_{17}H_{17}C1N_60_3$

Molecular Weight : 388.8

CAS number

43200-80-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

14 October 2009

10 DATE OF REVISION

16 July 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.9	Management of overdose statement updated
8	Sponsor details updated